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Descripti n

BACKGROUND OF THE INVENTION

Field of the invention

This invention relates to novel sulfoxide derivatives and processes for the preparation of the same.

Description of prior art

It is well known in the art to which the present invention relates that $H^+ + K^+ATPase$ plays a principal role in the final secretion mechanism of gastric acid in stomach cells [Scand. J. Gastroenterol., 14, 131-135 (1979)]. As a substance having $H^+ + K^+ATPase$ inhibitory activity, Norinium bromide is known [Proceeding of the Society for Experimental Biology and Medicine, 172, 308-315 (1983)].

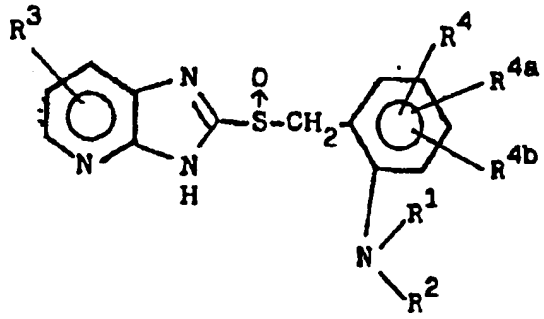
On the other hand, 2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-methoxy)-benzimidazole [trade-name : Omeprazole] has been developed as an antiulcer compound having $H^+ + K^+ATPase$ inhibitory activity [Am. J. of Physiol., 245, G64-71 (1983)]. It is also known from GB 2161160 that certain other heterocyclic sulphonyl compounds display gastric-secretion-inhibiting activity.

SUMMARY OF THE INVENTION

The present inventors have conducted extensive research and have now discovered that new sulfoxide derivatives having the specific formula exhibit excellent suppressive effects against the secretion of gastric acid owing to their specific $H^+ + K^+ATPase$ inhibitory effects.

Accordingly, an object of the present invention is to provide novel sulfoxide derivatives which is of value as an anti-ulcer agent.

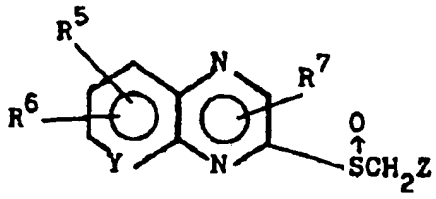
There is provided by the invention a sulfoxide derivative having the formula (I) :



(I)

wherein each of R^1 and R^2 independently is hydrogen or an alkyl group having 1 to 6 carbon atoms, and each of R^3, R^4, R^{4a} and R^{4b} independently is hydrogen, halogen, an alkoxy group having 1 to 6 carbon atoms which may be substituted with fluorine atom(s), or an alkyl group having 1 to 6 carbon atoms, or trifluoromethyl.

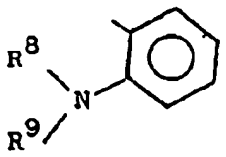
There is also provided by the invention a sulfoxide derivative having the formula (V) :



(V)

wherein each of R^5 and R^6 independently is hydrogen, halgoen, an alkyl group having 1 to 6 carbon atoms, or an alkoxy group having 1 to 6 carbon atoms, R^7 is hydrogen, an alkyl group having 1 to 6 carbon atoms, or an alkoxy group having 1 to 6 carbon atoms, Y is CH or N, and Z is unsubstituted or substituted 2-pyridyl or a

2-aminophenyl group having the formula (VI) :



(VI)

wherein each of R^8 and R^9 independently is hydrogen or an alkyl group having 1 to 6 carbon atoms, and the phenyl group may be substituted. The substituents attachable to the 2-pyridyl group and/or the phenyl group may be selected from the halogens, alkyl groups having 1 to 6 carbon atoms, and alkoxy groups having 1 to 6 carbon atoms.

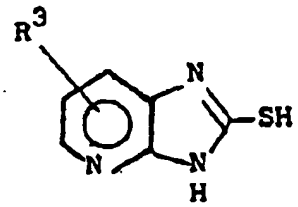
DETAILED DESCRIPTION OF THE INVENTION

Among the sulfoxide derivatives having the formula (I), sulfoxide derivatives wherein each of R^3, R^4, R^{4a} and R^{4b} is hydrogen are preferred. Each of R^1 and R^2 preferably is an alkyl group having 1 to 6 carbon atoms such as methyl or ethyl.

Representative exemples of the compounds of the formula (I) include :
2-(2-dimethylaminobenzylsulfinyl)imidazo[4,5-b]-pyridine ;
2-(2-dimethylaminobenzylsulfinyl)-7-methoxyimidazo-[4,5-b]-pyridine ;
2-(2-dimethylaminobenzylsulfinyl)-7-methylimidazo-[4,5-b]-pyridine ;
2-(2-diethylaminobenzylsulfinyl)imidazo[4,5-b]-pyridine ;
2-(2-dimethylamino-5-methylbenzylsulfinyl)imidazo-4,5-b]pyridine ;
2-(2-dimethylamino-4-chlorobenzylsulfinyl)imidazo-[4,5-b]pyridine ;
2-(2-dimethylamino-5-methoxybenzylsulfinyl)imidazo-[4,5-b]pyridine ;
2-(2-dimethylamino-6-methylbenzylsulfinyl)imidazo[4,5-b]pyridine ;
2-(2-dimethylamino-4-fluorobenzylsulfinyl)imidazo[4,5-b]pyridine ; and
2-(2-dimetbylaminobenzylsulfinyl)-6-methylimidazo[4,5-b]pyridine.

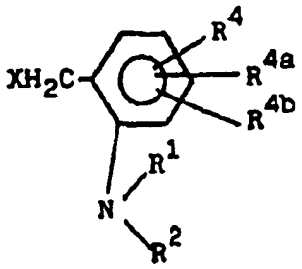
The sulfoxide derivative having the formula (I) can be advantageously prepared by a process which comprises :

reacting a mercapto derivative having the formula (II) :



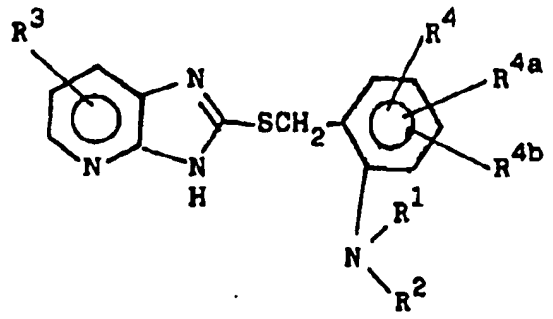
(II)

wherein R^3 has the same meaning as above, with a compound having the Formula (III) :



(III)

wherein each of R^1, R^2, R^4, R^{4a} and R^{4b} has the same meaning as above, and X is a reactive group, or a salt thereof to obtain a comp und having th Formula (IV) :



(IV)

wherein each of R^1, R^2, R^3, R^4, R^{4a} and R^{4b} has the same meaning as above, and

oxidizing the compound having the formula (IV),

The starting compound having the Formula (II) can be prepared by bringing a diaminopyridine or its derivative into contact potassium xanthogenate in an alcoholic solvent.

The reactive group (X) of the compound having the formula (III) can be a halogen atom such as chlorine or bromine ; a sulfonyloxy group such as methylsulfonyloxy or tolunsulfonyoxy ; or acetoxy.

The reaction of the compound (II) and the compound (III) can be performed at a temperature from room temperature to the reflux temperature for 30 min. to 24 hrs., in an inert solvent such as benzene, ethanol or acetone. The reaction can be carried out in the presence of an alkali agent such as NaOH, KOH, K_2CO_3 or $NaHCO_3$, for trapping an acid produced in the reaction.

The salt of the compound (III) can be an inorganic acid salt such as hydrochloride or sulfate, or an organic acid salt such as benzoate.

The oxidation of the compound (IV) can be performed in the conventional manner. For instance, the compound (IV) can be oxidized using an oxidizing agent such as hydrogen peroxide, an organic peroxide (e.g., m-chloroperbenzoic acid), or sodium hyprochlorite. The reaction can be performed in an inert solvent such as chloroform, dichloromethane, methanol, or ethyl acetate at a temperature ranging from −30°C to 50°C, preferably −15°C to 5°C.

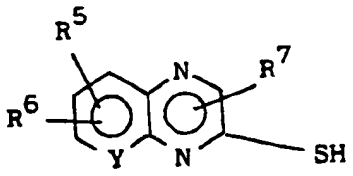
Among the sulfoxide derivatives having the formula (V), sulfoxide derivatives wherein each of R^5, R^6 and R^7 is hydrogen are preferred. Each of R^8 and R^9 preferably is an alkyl group having 1 to 6 carbon atoms such as methyl or ethyl.

Representative examples of the compounds of the formula (V) include :

2-(2-pyridylmethylsulfinyl)quinoxaline ;
3-methyl-2-(2-pyridylmethylsulfinyl)quinoxaline ;
2-[2-(4-methoxypyridyl)methylsulfinyl]-3-methyl-quinoxaline ;
3-methyl-2-[2-(2-methylpyridyl)methylsulfinyl]-quinoxaline ;
6,7-dimethyl-2-(2-pyridylmethylsulfinyl)quinoxaline ;
2-methyl-3-(2-pyridylmethylsulfinyl)pyrido[2,3-b]-pyrazine ;
2-(2-dimethylaminobenzylsulfinyl)quinoxaline ;
2-(2-dimethylaminolbenzylsulfinyl)-3-methyl-quinoxaline ;
2-(2-dimethylaminobenzylsulfinyl)-3,6,7-trimethyl-quinoxaline ;
2-(2-dimethylamino-3-methylbenzylsulfinyl)-3-methyl-quinoxaline ;
2-(2-dimethylamino-5-methylbenzylsulfinyl)-3-methyl-quinoxaline ;
2-(2-dimethylamino-5-methoxybenzylsulfinyl)-3-methylquinoxaline ;
2-(2-diethylaminobenzylsulfinyl)quinoxaline ;
7-chloro-2-(2-pyridylmethylsulfinyl)quinoxaline ;
6,7-dichloro-2-(2-dimethylaminobenzylsulfinyl)-quinoxaline ;
2-(2-dimethylamino-4-chlorobenzylsulfinyl)-3-methyl-quinoxaline ;
2-(2-dimethylaminobenzylsulfinyl)-6-methoxyquinoxaline ; and
2-(2-dimethylaminobenzylsulfinyl)-3-methoxyquinoxaline.

The sulfoxide derivative having the formula (V) can be advantageously prepared by a process which comprises :

reacting a mercapt derivative having th f rmula (VII) :

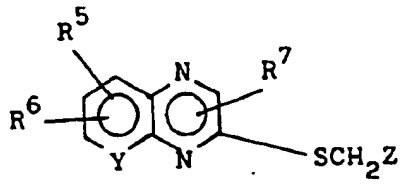


(VII)

wherein each of R^5, R^6, R^7 and Y has the same meaning as above, with a compound having the formula (VIII) :

$$QCH_2Z$$

wherein Z has the same meaning as above, and Q is a reactive group, or a salt thereof to obtain a compound having the formula (IX) :



(IX)

wherein each of R^5, R^6, R^7, Y and Z has the same meaning as above, and oxidizing the compound having the formula (IX).

The starting compound having the formula (VII) can be prepared from a diamino compound in the conventional manner. For instance, 2-mercapto-3-methylquinoxaline can be prepared by a process described in J. Org. Chem., 21, 470 (1956).

The reactive group (Q) of the compound having the formula (VIII) can be a halogen atom such as chlorine or bromine ; a sulfonyloxy group such as methylsulfonyloxy or toluensulfonyl ; or acetoxy.

The reaction of the compound (VII) and the compound (VIII) can be performed at a temperature from room temperature to the reflux temperature for 30 min. to 24 hrs., in an inert solvent such as benzene, ethanol or acetone. The reaction can be carried out in the presence of an alkali agent such as NaOH, KOH, K_2CO_3 or $NaHCO_3$, for trapping an acid produced in the reaction.

The salt of the compound (VIII) can be an inorganic acid salt such as hydrochloride or sulfate, or an organic acid salt such as benzoate.

The oxidation of the compound (IX) can be performed in the conventional manner. For instance, the compound (IX) can be oxidized using an oxidizing agent such as hydrogen peroxide, an organic peroxide (e.g., m-chloroperbenzoic acid), or sodium hypochlorite. The reaction can be performed in an inert solvent such as chloroform, dichloromethane, methanol, or ethyl acetate at a temperature ranging from −30°C to 50°C, preferably −15°C to 5°C.

Accute toxicity of the sulfoxide derivatives of the formula (I) or (V) have been determined in oral administration. It has been confirmed by observation of three days after oral administration to dog that these compounds show no noticeable side-effects at a dose of 100 mg/kg.

Further, it has been confirmed that the sulfoxide derivatives of the formula (I) or (V) according to the invention are of value as a cytoprotective agent for gastrointestinal tract and can be utilized for the treatment or prevention of a non-gastric-acid-induced, non-traumatically-induced, non-neoplastic gastrointestinal inflammatory disease in a mammal suffering from or particularly susceptible to the development of said disease, as disclosed in U.S. Patent No. 4,359,465 (Ruwart).

The anti-ulcer agent for gastrointestinal tract containing a sulfoxide derivative of the formula (I) or (V) can be administered orally or parenterally. Examples of the preparation forms for oral administration include tablets, capsules powder, granules, and syrup. In the formulation of these preparations, there can be used excipients, disintegrants, binders, lubricants, pigments, diluents and the like which are commonly employed in the art. Examples of the excipients include dextrose and lactose. Examples of th disintegrants include starch and carb xymethylcellulose. Examples of the lubricants include magnesium stearate and talc. Examples f the binders include hydroxypropylcellulose, gelatin and polyvinylpyrrolidone.

The dose is g nerally n t more than 500 mg/day, preferably about 100 µg/day to 300 mg/day, for an adult.

The dose can be either increased or decreased depending upon the age and other conditions.

The present invention is further described by the following examples.

(1) $H^+ + K^+$ATPase inhibitory effect

Following the method of Forte et al [J. Applied Physiol., 32, 714-717 (1972)], gastric acid secretory cells of a rabbit gastric mucosa were isolated and vesicle containing $H^+ + K^+$ATPase was prepared by centrifuging the cells in Ficoll of discontinuous density gradient. After the enzyme was incubated at room temperature for 25 min. in 0.5 mℓ of a solution which contained 5 mM of an imidazole buffer (pH 6.0) and 2×10^{-4} M of each test compound, the mixture was heated to 37°C at which it was allowed to stand for further 5 min. To the mixture was added 0.5 mℓ of a solution which contained 4 mM of magnesium chloride, 80 mM of an imidazole buffer (pH 7.4), 20 mM of potassium chloride and 4 mM of ATP. The resulting mixture was caused to react at 37°C for 15 min., and 1 mℓ of a 24% solution of trichloroacetic acid was then added to terminate the reaction. The inorganic phosphorus liberated was quantitatively analyzed by the method proposed by Taussky and Shorr [J. Biol. Chem., 202, 675-685 (1953)). The K^+-dependent activity of the ATPase was determined by substracting its activity obtained when no potassium chloride was contained. The results are set forth in Table 1 in which Compound Nos. 1-7 are the sulfoxide derivatives prepared in the hereinafter-described Examples 1-7, respectively.

Table 1

Test Compound No.	$H^+ + K^+$ATPase Inhibitory Effect (%)
1	92.3
2	96.8
3	99.5
4	89.4
5	100
6	100
7	80.8

(2) Inhibitory action against secretion of gastric acid

Male Donryu rats having a body weight of 200 to 250 g and fasting (while allowing free access to water) for 24 hours were employed for the present test which was performed in accordance with the conventional method [Shay, H. et al, Gastroenterology, 5, 43-61 (1945)].

Under ether anesthesia, the pylorus of the rat was ligated and each tast compound was administered intraduodenally. Four hours later, each rat was killed and the stomach was removed to collect the gastric juice. The inhibitory action was determined by comparing the acid output which was obtained by titration to pH 7.0 with 0.1-N NaOH by means of an automatic titrator, with the corresponding value of a control rat prepared in the same manner except that a vehicle alone was administered. The results are set forth in Table 2.

Table 2

Test Compound No.	Dose (mg/kg)	Suppresive action against secretion of gastric acid (%)
1	100	95.1
	30	79.0
	10	53.0
2	100	54.8
3	100	54.7
4	100	96.7
5	100	55.1
6	100	89.6
7	100	46.9
Cimetidine (for reference)	100	80.3
	30	59.1
	10	25.3

Remark: Cimetidine (tradename of N-cyano-N'-methyl-N"-[2-[[(5-methyl-1H-imidazol-4-yl)methyl]thio]ethyl]-guanidine)

(3) Inhibitory actions on gastric lesion models

Two different types of gastric lesion models were induced in male Donryu rats (180 to 240 g) which had been deprived of food but allowed free acess to water for 24 to 48 hours prior to experiments.

(a) Water-immersion stress-induced erosions :

Rats fasted for 24 hours before experiments were placed in a restraint cage. The animals were immersed vertically to the level of the xiphoid process in a water bath (21°C) for 7 hours and then killed. The stomach of each rat was removed and inflated by injecting 10 mℓ of 1% formalin to fix the inner and outer layers of the gastric walls. This formalin treatment was performed in all of the following experiments. Subsequently, the stomach was incised along a greater curvature and examined for any erosion in the glandular portion. Each test compound or a vehicle alone was given orally 10 minutes before stressing.

(b) HCℓ-ethanol-induced erosions

A hydrochloric acid-ethanol solution (150 mM HCℓ in 60% ethanol) was given orally to rats in a dose of 1 mℓ/200g, which rats had been fasted for 24 hours before experiments. One hour later, each animal was killed and the stomach was examined for any erosion in the glandular portion. Each test compound or a vehicle alone was given orally 30 minutes before ethanol treatment.

The results are shown in Tables 3 and 4.

Table 3

Test Compound No.	Dose (mg/kg)	Inhibition on Water-Immersion stress-induced erosions (%)
1	100	87
	30	66
Cimetidine (for reference)	200	87
	60	49

Table 4

Test Compound No.	Dose (mg/kg)	Inhibition on HCℓ-Ethanol-induced Erosions (%)
1	30	97
	10	37

The processes for the preparation of the sulfoxide derivatives of the invention are further described by the following examples.

Example 1

Synthesis of 2-(2-Dimethylaminobenzylsulfinyl)-imidazo[4,5-b]pyridine (Compound No. 1)

(1) Preparation of 2-mercaptoimidazo[4,5-b]pyridine

A mixture of 5 g of 2,3-diaminopyridine, 14.3 g of potassium xantogenate, 50 mℓ of ethanol and 10 mℓ of water was heated under reflux for 8 hrs., and then the solvents were removed from the reaction mixture under reduced pressure. The resulting solid residue was washed with acetone. The solid was then dissolved in water. The resulting aqueous solution was made acidic by addition of acetic acid to give a crystalline precipitate. The precipitate was collected by filtration and washed successively with water and ther to give 5 g of 2-mercaptoimidazo[4,5-b]pyridin , m.p. : higher than 250°C.

(2) Preparation of 2-(2-dimethylaminobenzylthi)-imidazo[4,5-b]pyridine

T a s luti n of 1.71 g of sodium hydroxide in a mixture of 100 mℓ of ethanol and 5 mℓ f water was added 3.0 g of 2-mercaptoimidazo[4,5-b]pyridine. T thus obtained mixture was added 4.09 g of 2-dimethylaminoben-

zyl chl rid hydrochloride, and thus btained mixture was stirred at room temperature for 17.5 hrs. The solvent was then removed under reduced pressur , and the resulting residue was extracted with thyl acetat .

The organic layer was washed successively with 5% aque us sodium hydroxide soluti n, water and saturated aqueous sodium chlorid soluti n, and then dried over s dium sulfate. The sodium sulfate was removed by filtration, and the solvent was removed to giv a residue. The residue was warmed in ether, and the insolubles were removed by fitration.

The filtrate was concentrated to give 2.95 g of 2-(2-dimethylaminobenzylthio)imidazo[4,5-b]pyridine as a white powder.

^{1}H NMR ($CDCl_3$) δ : 2.96 (s, 6H), 4.44 (s, 2H), 7.0-8.2 (m, 7H)

(3) Preparation of 2-(2-dimethylaminobenzylsulfinyl)imidazo[4,5-b]pyridine (Compound No. 1)

In 50 mℓ of chloroform was dissolved 1.5 g of 2-(2-dimethylaminobenzylthio)imidazo[4,5-b]pyridine. To the resulting solution under chilling to −10°C was added portionwise 1.36 g of m-chloroperbenzoic acid (purity : 80%). The reaction mixture was washed successively with saturated aqueous $NaHCO_3$ solution, water and saturated aqueous sodium chloride solution, and then dried over sodium sulfate. The sodium sulfate was removed by filtration, and the solvent was removed to give a solid residue. The residue was recrystallized from ethanol to give 1.15 g of 2-(2-dimethylaminobenzylsulfinylimidazo[4,5-b]pyridine as a white powder, m.p. 135-136°C.

IRν_{max}^{KBr}cm^{-1} : 1590, 1400, 1260, 1070, 1040, 940, 755

^{1}H NMR ($CDCl_3$) δ : 2.60 (s, 6H), 4.48 and 4.84 (each d, 2H, J=14Hz), 6.8-8.7 (m, 7H)

Example 2

Synthesis of 2-(2-Pyridylmethylsulfinyl)quinoxaline (Composed No. 2)

(1) Preparation of 2-(2-pyridylmethylthio)quinoxaline

In 50 mℓ of acetone was dissolved 2.0 g of 2-mercaptoquinoxaline. To the solution were added 2.02 g of 2-picolyl chloride hydrochloride, 4.0 g of potassium carbonate and 5 mℓ of water. The resulting mixture was stirred at room temperature for 0.5 hr., and the solvent was removed under reduced pressure. The residue was extracted with chloroform after addition of chloroform and water. The organic layer was separated and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was placed under reduced pressure to remove the solvent. To the residue were added 20 mℓ of ethanol and 1.03 mℓ of conc. hydrochloric acid and then added ether. Thus precipitated crystals were washed with ethanol-ether (1 : 1) and dried under reduced pressure to give 2.09 g of 2-(2-pyridylmethylthio)quinoxaline hydrochloride as a yellow crystalline powder.

^{1}H NMR (CD_3OD) δ : 4.97 (s, 2H), 7.6-8.7 (m, 7H), 8.73 (s, 1H), 8.84 (m, 1H)

(2) Preparation of 2-(2-pyridylmethylsulfinyl)quinoxaline (Compound No. 2)

In a mixture of 20 mℓ of chloroform and 5 mℓ of methanol was dissolved 2.51 g of 2-(2-pyridylmethylthio)quinoxaline hydrochloride. To the chilled solution kept at a temperature of lower than 0°C (temperature of solution) was portionwise added 1.95 g of m-chloroperbenzoic acid (purity : 70%). After the reaction was complete, chloroform and saturated aqueous $NaHCO_3$ solution were added to the reaction mixture. The organic layer was separated and dried over sodium sulfate. The sodium sulfate was then removed by filtration, and the solvent was evaporated under reduced pressure from the filtrate. The residue was purified by silica gel column chromatography (acetone/hexane), and recrystallized from ethanol/ether to give 0.27 g of 2-(2-pyridylmethylsulfinyl)quinoxaline as a pale brown crystalline powder, m.p. 117-122°C (decompn.).

IRν_{max}^{KBr}cm^{-1} : 1590, 1470, 1430, 1360, 1200, 1200, 1080, 1050, 995, 960, 765, 745

^{1}H NMR ($CDCl_3$)δ : 4.43 and 4.70 (each d, 2H, J=14Hz), 7.0-8.2 (m, 7H), 8.38 (m, 1H), 9.06 (s, 1H)

Example 3

Synthesis of 3-Methyl-2-(2-pyridylmethylsulfinyl)quinoxaline (Compound No. 3)

(1) Preparation of 3-methyl-2-(2-pyridylmethylthio)quinoxaline

In a mixture of 70 mℓ of acetone and 7 mℓ of water were suspended 1.9 g of 2-mercapto-3-methylquinoxaline

and 1.95 g of 2-picolyl chloride hydrochloride. To the suspension was added 4.0 g of potassium carbonate. The resulting mixture was stirred at room temperature for 1 hr., and the solvent was removed under reduced pressure. The residue was extracted with chloroform after addition of chloroform and water. The organic layer was separated and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was placed under reduced pressure to remove the solvent. The residue was dissolved in 20 mℓ of ethanol. To the solution under chilling with ice were successively added 3.2 mℓ of 5.2N ethanolic hydrochloric acid and ether to precipitate crystals. The crystals were collected by filtration to give 2.25 g of 3-methyl-2-(2-pyridylmethylthio)quinoxaline hydrochloride as a violet crystalline powder.

^{1}H NMR (CD_3OD)δ : 2.68 (s, 3H), 4.98 (s, 2H),
7.5-8.7 (m, 7H), 8.84 (m, 1H)

(2) Preparation of 3-methyl-2-(2-pyridylmethylsulfinyl)quinoxaline (Compound No. 3)

In a mixture of 36 mℓ of chloroform and 18 mℓ of methanol was dissolved 2.6 g of 3-methyl-2-(2-pyridylmethylthio)quinoxaline hydrochloride. To the chilled solution kept at a temperature of lower than 0°C (temperature of solution) was added 1.77 g of m-chloroperbenzoic acid (purity 70%). After the reaction was complete, chloroform and saturated aqueous $NaHCO_3$ solution were added to the reaction mixture under chilling. The organic layer was separated and dried over sodium sulfate. The sodium sulfate was then removed by filtration, and the solvent was evaporated under reduced pressure from the filtrate. The residue was purified by silica gel column chromatography (chloroform/methanol), and recrystallized from ether/hexane to give 1.63 g of 3-methyl-2-(2-pyridylmethylsulfinyl)quinoxaline as an orange crystalline powder, m.p. 85-88°C (decompn.).

IRν_{max}^{KBr}cm^{-1} : 1595, 1470, 1435, 1095, 1080, 1035, 770

^{1}H NMR ($CDC\ell_3$)δ : 2.73 (s, 3H),
4.55 and 4.71 (each d, 2H, J=13Hz),
7.0-8.3 (m, 7H), 8.39 (m, 1H)

Example 4

Synthesis of 2-Methyl-3-(2-pyridylmethylsulfinyl)pyrido[2,3-b]pyrazine (Compound No. 4)

(1) Preparation of 2-methyl-3-(2-pyridylmethylthio)pyrido[2,3-b]pyrazine

To 1.67 g of 3-mercapto-2-methylpyrido[2,3-b]pyrazine were added 10 mℓ of ethanol and a solution of 1.15 g of 2-picolyl chloride hydrochloride and 0.67 g of sodium hydroxide. The obtained mixture was heated under refluxing for 1.5 hrs, and then the solvent was removed under reduced pressure. The residue was extracted with ethyl acetate. The extract was washed with water and saturated aqueous sodium chloride solution, and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was placed under reduced pressure to remove the solvent. The residue was dissolved in 20 mℓ of acetonitrile, and the insolubles were removed by filtration. The filtrate was concentrated to give 1.5 g of 2-methyl-3-(2-pyridylmethylthio)pyrido[2,3-b]pyrazine as a brown oil.

^{1}H NMR ($CDC\ell_3$)δ : 2.74 (s, 3H), 4.72 (s, 2H),
7.0-9.0 (m, 7H)

(2) Preparation of 2-methyl-3-(2-pyridylmethylsulfinyl)pyrido[2,3-b]pyrazine (Compound No. 4)

In 14 mℓ of chloroform was dissolved 1.4 g of 2-methyl-3-(2-pyridylmethylthio)pyrido[2,3-b]pyrazine. To the solution under chilling with ice was added portionwise 1.1 g of m-chloroperbenzoic acid (purity : 80%). The reaction mixture was then left to have room temperature, and poured into saturated aqueous $NaHCO_3$ solution. The aqueous mixture was extracted with chloroform. The chloroform layer was washed with water and saturated aqueous sodium chloride solution, and dried over sodium sulfate. The sodium sulfate was then removed by filtration, and the solvent was evaporated under reduced pressure from the filtrate. The residue was purified by silica gel column chromatography (chloroform/methanol), to give 420 mg of 2-methyl-3-(2-pyridylmethylsulfinyl)pyrido[2,3-b]pyrazine as a brown crystalline powder, m.p. 120-125°C (decompn.).

IRν_{max}^{KBr}cm^{-1} : 3460, 1580, 1440, 1270, 1080, 1069, 795

^{1}H NMR ($CDC\ell_3$)δ : 2.78 (s, 3H),
4.57 and 4.74 (each d, 2H, J=13Hz),
7.0-7.9 (m, 4H), 8.20-8.38 (m, 1H),
8.50 (dd, 1H, J=2Hz, 8Hz),
9.16 (dd, 1H, J=2Hz, 4Hz)

Exampl 5

Synthesis f 2-(2-Dimethylaminobenzylsulfinyl)quinoxalin (Compound No. 5)

(1) Preparation of 2-(2-dimethylaminobenzylthi)quin xaline

To a solution of 1 g of 2-mercaptoquinoxaline in 40 mℓ of ethanol was added a solution of 530 mg of sodium hydroxide in 2 mℓ of water, and subsequently added 1.27 g of 2-dimethylaminobenzyl chloride hydrochloride. The resulting mixture was stirred at room temperature for 18 hrs., and the solvent was removed under reduced pressure. The residue was extracted with ethyl acetate. The organic layer was washed successively with 5% aqueous sodium hydroxide solution, water, and saturated aqueous sodium chloride solution, and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was placed under reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography (hexane/acetone) to give 1.5 g of 2-(2-dimethylaminobenzylthio)quinoxaline as a yellow oil.

^{1}H NMR ($CDC\ell_3$)δ : 2.76 (s, 6H), 4.72 (s, 2H),
6.8-7.6 (m, 9H)

(2) Preparation of 2-(2-dimethylaminobenzylsulfinyl)quinoxaline (Compound No. 5)

In 50 mℓ of chloroform was dissolved 1.47 g of 2-(2-dimethylaminobenzylthio)quinoxaline. To the chilled solution kept at −10°C was portionwise added 1.54 g of m-chloroperbenzoic acid (purity : 80%). To the reaction liquid were washed successively with saturated aqueous $NaHCO_3$ solution, water and saturated aqueous sodium chloride solution, and dried over sodium sulfate. The sodium sulfate was then removed by filtration, and the solvent was evaporated under reduced pressure from the filtrate. The residue was purified by silica gel column chromatography (hexane/acetone) to give 330 mg of 2-(2-dimethylaminobenzylsulfinyl)quinoxaline as a yellow powder, m.p. 114-115°C.

IRν_{max}^{KBr}cm^{-1} : 1485, 1445, 1080, 1045, 945, 760

^{1}H NMR ($CDC\ell_3$)δ : 2.40 (s, 6H),
4.46 and 4.66 (each d, 2H, J=14Hz),
6.9-8.2 (m, 9H)

Example 6

Synthesis of 2-(2-Dimethylaminobenzylsulfinyl)-3-methylquinoxaline (Compound No. 6)

(1) Preparation of 2-(2-dimethylaminobenzylthio)3-methylquinoxaline

In a mixture of 50 mℓ of acetone and 5 mℓ of water were suspended 2.80 g of 2-mercapto-3-methylquinoxaline, 3.28 g of 2-dimethylaminobenzyl chloride hydrochloride, and 8.0 g of potassium carbonate. The resulting mixture was stirred at room temperature for 40 min., and the solvent was removed under reduced pressure. The residue was extracted with chloroform after addition of chloroform and water. The organic layer was separated and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was placed under reduced pressure to remove the solvent. The residue was diluted with 50 mℓ of ethanol. To the solution under chilling with ice were successively added 1.33 mℓ of conc. hydrochloric acid and ether to precipitate crystals. The crystals were collected by filtration to give 4.56 g of 2-(2-dimethylaminobenzylthio)-3-methylquinoxaline hydrochloride as a dark brown crystalline powder.

^{1}H NMR ($CD_3OD/CDC\ell_3$)δ : 2.67 (s, 3H), 3.46 (s, 6H),
5.00 (s, 2H), 7.4-8.1 (m, 8H)

(2) Preparation of 2-(2-dimethylaminobenzylsulfinyl)-3-methylquinoxaline (Compound No. 6)

In a mixture of 10 mℓ of chloroform and 10 mℓ of methanol was dissolved 1.73 g of 2-(2-dimethylaminobenzylthio)-3-methylquinoxaline hydrochloride. To the chilled solution kept at a temperature of lower than 0°C (temperature of solution) was portionwise added 1.14 g of m-chloroperbenzoic acid (purity : 80%). After the reaction was complete, chloroform and saturated aqueous $NaHCO_3$ solution were added to the reaction mixture. The organic layer was separated and dried over sodium sulfate. The sodium sulfate was then removed by filtration, and the solvent was evaporated under reduced pressure from the filtrate. The residue was purified by silica gel column chromatography (chloroform/methanol), and recrystallized from ethyl acetate/hexane to give 0.51 g of 2-(2-dimethylaminobenzylsulfinyl)-3-methylquinoxaline as a pale brown crystalline powder, m.p. 68-70°C (decompn.).

IRν_{max}^{KBr}cm^{-1} : 1590, 1160, 1090, 1080, 1070, 1045, 945, 760

^{1}H NMR ($CDC\ell_3$)δ : 2.42 (s, 6H), 2.49 (s, 3H),
4.44 and 4.73 (each d, 2H, J=12Hz),
6.8-8.3 (m, 8H)

Example 7

Synthesis of 2-(2-Dimethylaminobenzylsulfinyl)-3,6,7-trimethylquinoxalin (Compound No. 7)

(1) Preparation of 2-(2-dimethylaminobenzylthio)3,6,7-trimethylquinoxaline

To a mixture of 50 mℓ of acetone and 5 mℓ of water were added 4.08 g of 2-mercapto-3,6,7-trimethylquinoxaline, 4.12 g of 2-dimethylaminobenzyl chloride hydrochloride, and 10.0 g of potassium carbonate. The resulting mixture was stirred at room temperature for 2 hrs., and the solvent was removed under reduced pressure. To the residue were added water and chloroform. After the insolubles were removed by filtration, the organic layer was separated and dried over sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was placed under reduced pressure to remove the solvent. To the residue was added hexane, and the insolubles were removed by filtration. The filtrate was dried under reduced pressure to give 6.48 g of 2-(2-dimethylaminobenzylthio)-2,6,7-trimethylquinoxaline hydrochloride as a pale orange crystalline powder.

^{1}H NMR ($CDC\ell_3$)δ : 2.43 (s, 6H), 2.61 (s, 3H),
2.75 (s, 6H), 4.73 (s, 2H),
6.8-7.8 (m, 6H)

(2) Preparation of 2-(2-dimethylaminobenzylsulfinyl)-3,6,7-trimethylquinoxaline (Compound No. 7)

In a mixture of 35 mℓ of chloroform and 3 mℓ of methanol was dissolved 3.71 g of 2-(2-dimethylaminobenzylthio)-3,6,7-trimethylquinoxaline. To the chilled solution kept at a temperature of lower than 0°C (temperature of solution) was slowly added 2.45 g of m-chloroperbenzoic acid (purity : 80%). After the reaction was complete, chloroform and saturated aqueous $NaHCO_3$ solution were added to the reaction mixture. The organic layer was separated and dried over sodium sulfate. The sodium sulfate was then removed by filtration, and the solvent was evaporated under reduced pressure from the filtrate. The residue was purified by silica gel column chromatography (acetone/hexane). The eluate was concentrated and the resulting residue was crystallized from ether/hexane to give 1.12 g of 2-(2-dimethylaminobenzylsulfinyl)-3,6,7-trimethylquinoxaline as a yellow crystalline powder, m.p. 83-88°C (decompn.).

IRν_{max}^{KBr}cm^{-1} : 2930, 1490, 1480, 1445, 1090, 1070, 1050, 870, 760

^{1}H NMR ($CDC\ell_3$)δ : 2.46 (s, 9H), 2.51 (s, 6H),
4.44 and 4.71 (each d, 2H, J=12Hz),
6.8-7.4 (m, 4H),
7.76 and 8.00 (each s, 2H)

Example 8

Synthesis of 2-(2-Diethylaminobenzylsulfinyl)-3-methylquinoxaline

(1) Preparation of 2-(2-diethylaminobenzylthio)-3-methylquinoxaline

To a solution of 0.73 g of sodium hydroxide in a mixture of 2 mℓ of water and 50 mℓ of ethanol were added successively 1.5 g of 2-mercapto-3-methylquinoxaline and 1.99 g of 2-diethylaminobenzyl chloride hydrochloride. The resulting mixture was stirred at room temperature for 3 hrs., and the solvent was removed under reduced pressure. The residue was extracted with ethyl acetate. The organic layer was washed successively with 5% aqueous sodium hydroxide solution, water and saturated aqueous sodium chloride solution, and then dried over sodium, sulfate. The sodium sulfate was removed by filtration, and the filtrate was placed under reduced pressure to remove the solvent. The residual oil was purified by silica gel column chromatography (hexane/acetone) to give 1.74 g of 2-(2-diethylaminobenzylthio)-3-methylquinoxaline as a yellow oil.

^{1}H NMR ($CDC\ell_3$) δ : 1.04 (t, 6H, J=8Hz), 2.64 (s, 3H),
3.04 (q, 4H, J=8Hz), 4.76 (s, 2H),
6.8-8.0 (m, 8H)

(2) Preparation of 2-(2-diethylaminobenzylsulfinyl)-3-methylquinoxaline

In 50 mℓ of chloroform was dissolved 1.7 g of 2-(2-diethylaminobenzylthio)-3-methylquinoxaline. To the chilled solution kept at −10°C was portionwise added 1.21 g of m-chloroperbenzoic acid (purity : 80%). The reaction liquid was then washed successively with saturated aqueous $NaHCO_3$ solution, water and saturated aqueous sodium chloride solution, and dried over sodium sulfate. The sodium sulfate was then removed by filtration, and the solvent was evaporated under reduced pressure from the filtrate. The residual oil was purified by silica g l column chromatography (hexane/ac tone) to giv 1.2 g f 2-(2-diethylamin b nzylsulfinyl)-3-methylquinoxaline as a yellow oil.

^{1}H NMR ($CDC\ell_3$)δ : 0.96 (t, 6H, J=8Hz), 2.52 (s, 3H),
2,92 (q, 4H, J=8Hz),

4.44 and 4.70 (each d, 2H, J=12Hz),
6.8-8.4 (m, 8H)

Examples of the preparations using the sulfoxide derivative of the invention are described by the following examples.

Example 9 : Preparation in the form of pellet

A pellet (220 mg) containing :

active component	50 mg
lactose	103 mg
starch	50 mg
magnesium stearate	2 mg
hydroxypropylcellulose	15 mg

was obtained.

Example 10 : Preparation in the form of capsule

A gelatin-shell hard capsule containing 350 mg of the core portion consisting of :

active component	40 mg
lactose	200 mg
starch	70 mg
polyvinylpyrrolidone	5 mg
crystalline cellulose	35 mg

was obtained.

Example 11 : Preparation in the form of granules

One gram of granules containing :

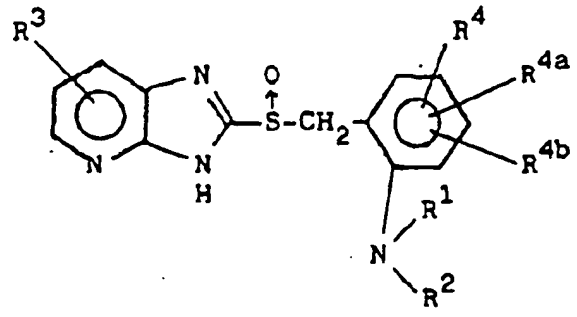
active component	200 mg
lactose	450 mg
corn starch	300 mg
hydroxypropylcellulose	50 mg

was obtained.

Claims

Claims for the Contracting States : BE, CH, DE, FR, GB, IT, LI, NL, SE

1. A sulfoxide derivative having the formula (I) :



(I)

wherein each of R^1 and R^2 independently is hydrogen or an alkyl group having 1 to 6 carbon atoms, and each of R^3, R^4, R^{4a} and R^{4b} independently is hydrogen, halogen, an alkoxy group having 1 to 6 carbon atoms, an alkyl group having 1 to 6 carbon atoms, trifluoromethyl, or a fluorine-atom-containing lower alkoxy

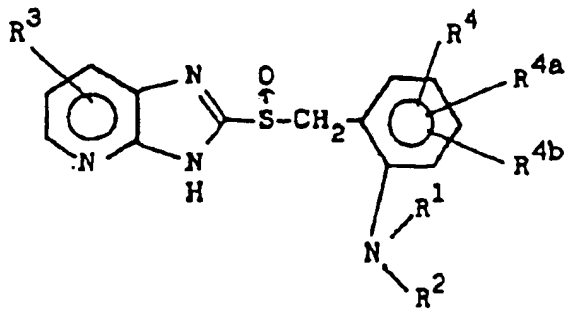
2. The sulfoxide derivative as claimed in claim 1, wherein each of R^3, R^4, R^{4a} and R^{4b} is hydrogen.

3. The sulfoxide derivative as claimed in claim 1, wher in each of R^1 and R^2 ind pendently is an alkyl group having 1 to 6 carbon atoms.

4. The sulfoxide derivative as claimed in claim 1, wherein each of R^1 and R^2 independently is methyl or ethyl.

5. The sulfoxide derivative as claimed in claim 1, wherein said derivative is 2-(2-dimethylaminobenzylsulfinyl)imidazo[4,5-b]pyridine.

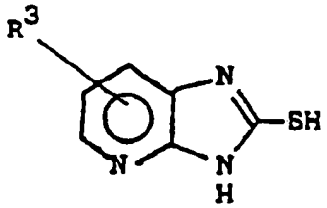
6. A process for the preparation of a sulfoxide derivative having the formula (I) :



(I)

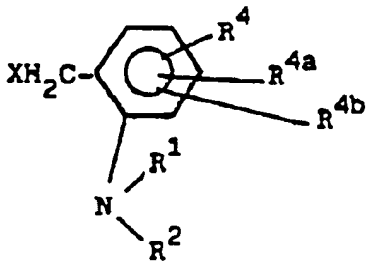
wherein each of R^1 and R^2 independently is hydrogen or an alkyl group having 1 to 6 carbon atoms, and each of R^3, R^4, R^{4a} and R^{4b} independently is hydrogen, halogen, an alkoxy group, containing 1-6 carbon atoms trifluoromethyl, or a fluorine atom-containing lower alkoxy group having 1 to 6 carbon atoms, or an alkyl group having 1 to 6 carbon atoms, which comprises :

reacting a mercapto derivative having the formula (II) :



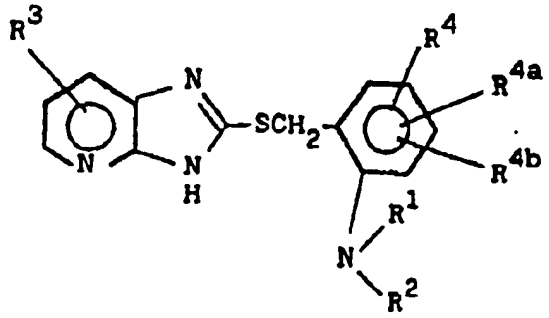
(II)

wherein R^3 has the same meaning as above, with a compound having the formula (III) :



(III)

wherein each of R^1, R^2, R^4, R^{4a} and R^{4b} has the sam meaning as above, and X is a reactiv group, or a salt thereof to obtain a compound having th formula (IV) :



(IV)

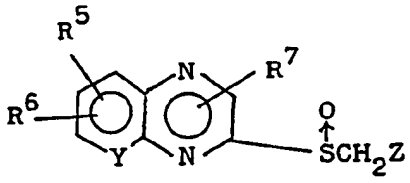
wherein each of R^1, R^2, R^3, R^4, R^{4a} and R^{4b} has the same meaning as above, and

oxidizing the compound having the formula (IV).

7. The process for the preparation of a sulfoxide derivative as claimed in claim 6, wherein said reactive group represented by X in the Formula (III) is a halogen atom, a sulfonyl group or acetoxy.

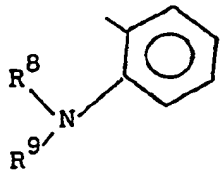
8. The proccess for the preparation of a sulfoxide derivative as claimed in claim 6, wherein said reaction between the mercapto derivative of the formula (II) and the compound of the formula (III) is performed in an inert solvent in the presence of an alkali agent.

9. A sulfoxide derivative having the formula (V) :



(V)

wherein each of R^5 and R^6 independently is hydrogen, halogen, an alkyl group having 1 to 6 carbon atoms, or an alkoxy group having 1 to 6 carbon atoms, R^7 is hydrogen, an alkyl group having 1 to 6 carbon atoms, or an alkoxy group having 1 to 6 carbon atoms, Y is CH or N, and Z is : unsubstituted 2-pyridyl ; or 2-pyridyl substituted with a halogen, an alkyl group-having 1 to 6 carbon atoms and /or an alkoxy group having 1 to 6 carbon atoms; or a 2-aminophenyl group having the formula (VI) :



(VI)

wherein each of R^8 and R^9 independently is hydrogen or an alkyl group having 1 to 6 carbon atoms, and the phenyl group may be substituted with a halogen, an alkyl group having 1 to 6 carbon atoms and /or an alkoxy group having 1 to 6 carbon atoms.

10. The sulfoxide derivative as claimed in claim 9, wherein each of R^5, R^6 and R^7 independently is hydrogen or methyl.

11. The sulfoxide derivative as claimed in claim 9, wherein each of R^8 and R^9 independently is an alkyl group having 1 to 6 carbon atoms.

12. The sulfoxide derivative as claimed in claim 9, wherein each of R^8 and R^9 independently is methyl or ethyl.

13. The sulfoxide derivative as claimed in claim 9, wherein said derivative is one selected from the group consisting of :

2-(2-pyridylmethylsulfinyl)quinoxaline ;

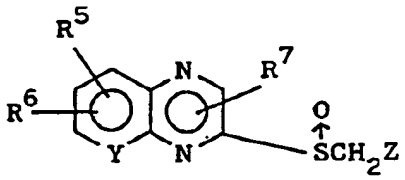
3-methyl-2-(2-pyridylmethylsulfinyl)quinoxalin ;

2-[2-(4-methoxypyridyl)methylsulfinyl]-3-methyl-quinoxaline ;

3-methyl-2-[2-(3-methylpyridyl)methylsulfinyl]-quinoxalin ;

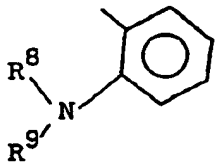
6,7-dimethyl-2-(2-pyridylmethylsulfinyl)quinoxaline ;
2-methyl-3-(2-pyridylmethylsulfinyl)pyrid [2,3-b]-pyrazine ;
2-(2-dimethylaminobenzylsulfinyl)quinoxaline ;
2-(2-dimethylamin lbenzylsulfinyl)-3-methyl-quinoxaline ;
2-(2-dimethylaminobenzylsulfinyl)-3,6,7-trimethyl-quinoxaline ;
2-(2-dimethylamino-3-methylbenzylsulfinyl)-3-methyl-quinoxaline ;
2-(2-dimethylamino-5-methylbenzylsulfinyl)-3-methyl-quinoxaline ;
2-(2-dimethylamino-5-methoxybenzylsulfinyl)-3-methylquinoxaline ; and
2-(2-diethylaminobenzylsulfinyl)quinoxaline.

14. A process for the preparation of a sulfoxide derivative having the formula (V) :



(V)

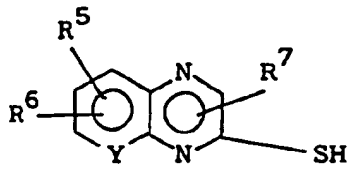
wherein each of R^5 and R^6 independently is hydrogen, halogen, an alkyl group having 1 to 6 carbon atoms, or an alkoxy group having 1 to 6 carbon atoms, R^7 is hydrogen, an alkyl group having 1 to 6 carbon atoms, or an alkoxy group having 1 to 6 carbon atoms, Y is CH or N, and Z is : unsubstituted 2-pyridyl ; or 2-pyridyl substituted with a halogen, an alkyl group having 1 to 6 carbon atoms and/or an alkoxy group having 1 to 6 carbon atoms; or a 2-aminophenyl group having the formula (VI) :



(VI)

wherein each of R^8 and R^9 independently is hydrogen or an alkyl group having 1 to 6 carbon atoms, and the phenyl group may be substituted with a halogen, an alkyl group having 1 to 6 carbon atoms and/or an alkoxy group having 1 to 6 carbon atoms ; which comprises :

reacting a mercapto derivative having the formula (VII) :

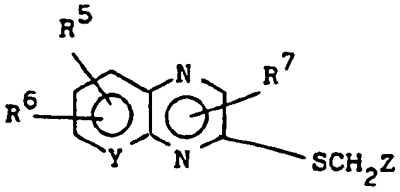


(VII)

wherein each of R^5, R^6, R^7 and Y has the same meaning as above, with a compound having the formula (VIII):

$$QCH_2Z$$

wherein Z has the same meaning as above, and Q is a reactive group, or a salt thereof to obtain a compound having the formula (IX) :



(IX)

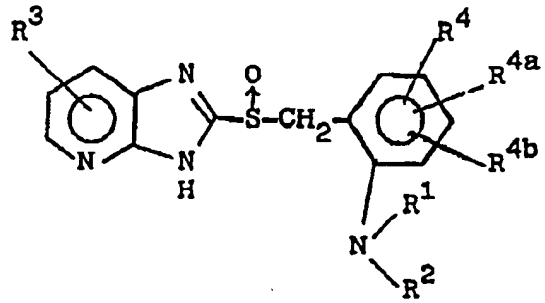
wherein each of R^5, R^6, R^7, Y and Z has the same meaning as above, and oxidizing the compound having the formula (IX).

15. The process for the preparation of a sulfoxide derivative as claimed in claim 14, wherein said reactive group represented by Q in the formula (VIII) is a halogen atom, a sulfonyl group or acetoxy.

16. The process for the preparation of a sulfoxide derivative as claimed in claim 14, wherein said reaction between the mercapto derivative of the formula (VII) and the compound of the formula (VIII) is performed in an inert solvent in the presence of an alkali agent.

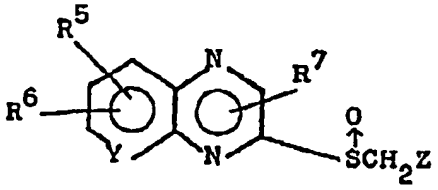
17. A pharmaceutical composition containing as an active ingredient a sulfoxide derivative having the formula (I) or (V) :

formula (I)

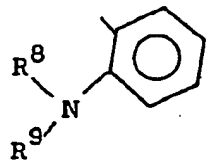


wherein each of R^1 and R^2 independently is hydrogen or an alkyl group having 1 to 6 carbon atoms, and each of R^3, R^4, R^{4a} and R^{4b} independently is hydrogen, halogen, an alkoxy group having 1 to 6 carbon atoms, trifluoromethyl, or a fluorine atom-containing lower a alkoxy group having 1 to 6 carbon atoms, or an alkyl group having 1 to 6 carbon atoms,

formula (V)



wherein each of R^5 and R^6 independently is hydrogen, halogen, an alkyl group having 1 to 6 carbon atoms, or an alkoxy group having 1 to 6 carbon atoms, R^7 is hydrogen, an alkyl group having 1 to 6 carbon atoms, or an alkoxy group having 1 to 6 carbon atoms, Y is CH or N, and Z is : unsubstituted 2-pyridyl ; or 2-pyridyl substituted with a halogen ; an alkyl group having 1 to 6 carb n atoms and/ r an alkoxy group having 1 to 6 carbon atoms; or a 2-aminophenyl group having the formula (VI) :

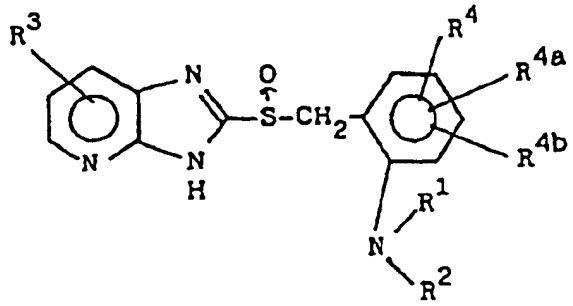


(VI)

wherein each of R^8 and R^9 independently is hydrogen or an alkyl group having 1 to 6 carbon atoms, and the phenyl group may be substituted with a halogen, an alkyl group having 1 to 6 carbon atoms and/or an alkyl group having 1 to 6 carbon atoms.

Claims for the Contracting State : ES

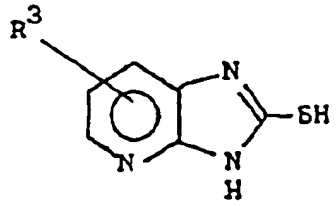
1. A process for the preparation of a sulfoxide derivative having the formula (I) :



(I)

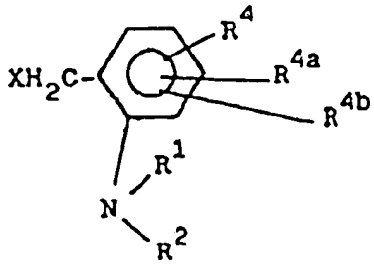
wherein each of R^1 and R^2 independently is hydrogen or an alkyl group having 1 to 6 carbon atoms, and each of R^3, R^4, R^{4a} and R^{4b} independently is hydrogen, halogen, an alkoxy group containing 1 to 6 carbon atoms, trifluoromethyl, or a fluorine atom-containing lower alkoxy group having 1 to 6 carbon atoms, or an alkyl group having 1 to 6 carbon atoms, which comprises :

reacting a mercapto derivative having the formula (II) :



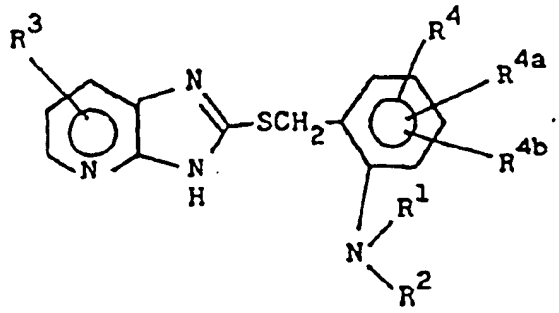
(II)

wherein R^3 has the same meaning as above, with a compound having the formula (III) :



(III)

wherein ach of R^1, R^2, R^4, R^{4a} and R^{4b} has the same meaning as above, and X is a r active group, or a salt thereof to obtain a compound having the formula (IV) :



(IV)

wherein each of R^1, R^2, R^3, R^4, R^{4a} and R^{4b} has the same meaning as above, and oxidizing the compound having the formula (IV).

2. The process for the preparation of a sulfoxide derivative as claimed in claim 1, wherein said reactive group represented by X in the Formula (III) in a halogen atom, a sulfonyl group or acetoxy.

3. The process for the preparation of a sulfoxide derivative as claimed in claim 1, wherein said reaction between the mercapto derivative of the formula (II) and the compound of the formula (III) is performed in an inert solvent in the presence of an alkali agent.

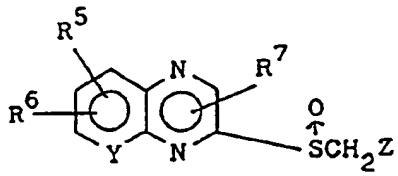
4. The process for the preparation of a sulfoxide derivative as claimed in claim 1, wherein each of R^3, R^4, R^{4a} and R^{4b} is hydrogen.

5. The process for the preparation of a sulfoxide derivative as claimed in claim 1, wherein each of R^1 and R^2 independently is an alkyl group having 1 to 6 carbon atoms.

6. The process for the preparation of a sulfoxide derivative as claimed in claim 1, wherein each of R^1 and R^2 independently is methyl or ethyl.

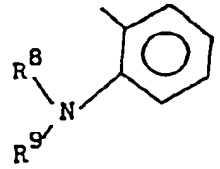
7. The process for the preparation of a sulfoxide derivative as claimed in claim 1, wherein said derivative is 2-(2-dimethylaminobenzylsulfinyl) imidazo[4,5-b]pyridine.

8. A process for the preparation of a sulfoxide derivative having the formula (V) :



(V)

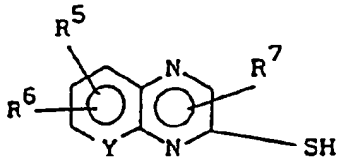
wherein each of R^5 and R^6 independently is hydrogen, halogen, an alkyl group having 1 to 6 carbon atoms, or an alkoxy group having 1 to 6 carbon atoms, R^7 is hydrogen, an alkyl group having 1 to 6 carbon atoms, or an alkoxy group having 1 to 6 carbon atoms, Y is CH or N, and Z is : unsubstituted 2-pyridyl ; or 2-pyridyl substituted with a halogen, an alkyl group having 1 to 6 carbon atoms and/or an alkoxy group having 1 to 6 carbon atoms; or a 2-aminophenyl group having the formula (VI) :



(VI)

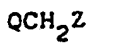
wherein each of R^8 and R^9 independently is hydrogen or an alkyl group having 1 to 6 carbon atoms, and the phenyl group may be substituted with a halogen, an alkyl group having 1 to 6 carbon atoms and/or an alkoxy group having 1 to 6 carbon atoms ; which comprises :

reacting a mercapto derivative having the formula (VII) :



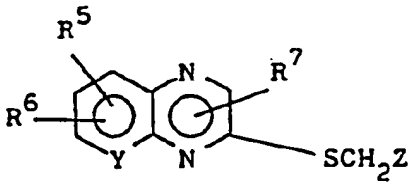
(VII)

wherein each of R^5, R^6, R^7 and Y has the same meaning as above,
with a compound having the formula (VIII) :



(VIII)

wherein Z has the same meaning as above, and Q is a reactive group,
or a salt thereof to obtain a compound having the formula (IX) :



(IX)

wherein each of R^5, R^6, R^7, Y and Z has the same meaning as above, and
oxidizing the compound having the formula (IX).

9. The process for the preparation of a sulfoxide derivative as claimed in claim 8, wherein said reactive group represented by Q in the formula (VIII) is a halogen atom, a sulfonyl group or acetoxy.

10. The process for the preparation of a sulfoxide derivative as claimed in claim 8, wherein said reaction between the mercapto derivative of the formula (VII) and the compound of the formula (VIII) is performed in an inert solvent in the presence of an alkali agent.

11. The process for the preparation of a sulfoxide derivative as claimed in claim 8, wherein each of R^5, R^6 and R^7 independently is hydrogen or methyl.

12. The process for the preparation of a sulfoxide derivative as claimed in Claim 8, wherein each of R^8 and R^9 independently is an alkyl group having 1 to 6 carbon atoms.

13. The process for the preparation of a sulfoxide derivative as claimed in Claim 8, wherein each of R^8 and R^9 independently is methyl or ethyl.

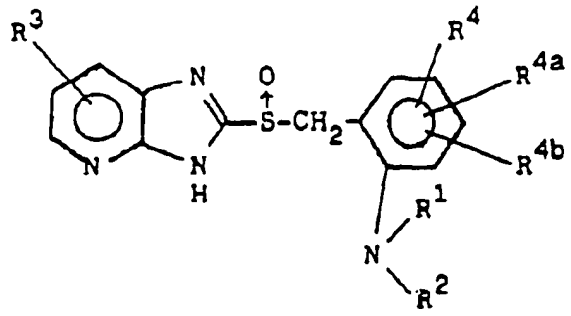
14. The process for the preparation of a sulfoxide derivative as claimed in claim 8, wherein said derivative is one selected from the group consisting of :

2-(2-pyridylmethylsulfinyl)quinoxaline ;
3-methyl-2-(2-pyridylmethylsulfinyl)quinoxaline ;
2-[2-(4-methoxypyridyl)methylsulfinyl]-3-methyl-quinoxaline ;
3-methyl-2-[2-(3-methylpyridyl)methylsulfinyl]-quinoxaline ;
6,7-dimethyl-2-(2-pyridylmethylsulfinyl)quinoxaline ;
2-methyl-3-(2-pyridylmethylsulfinyl)pyrido[2,3-b]-pyrazine ;
2-(2-dimethylaminobenzylsulfinyl)quinoxaline ;
2-(2-dimethylaminolbenzylsulfinyl)-3-methyl-quinoxaline ;
2-(2-dimethylaminobenzylsulfinyl)-3,6,7-trimethyl-quinoxaline ;
2-(2-dimethylamino-3-methylbenzylsulfinyl)-3-methyl-quinoxaline ;
2-(2-dimethylamino-5-methylbenzylsulfinyl)-3-methyl- quinoxaline ;
2-(2-dimethylamino-5-methoxybenzylsulfinyl)-3-methylquinoxaline ; and
2-(2-diethylaminobenzylsulfinyl)quinoxaline.

Ansprüche

Patentansprüche für die Vertragstaaten : BE, CH, DE, FR, GB, IT, LI, NL, SE

1. Sulfoxidderivat mit der Formel (I) :



(I)

worin jeder von R^1 und R^2 unabhängig Wasserstoff oder eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen ist, und jeder von R^3, R^4, R^{4a} und R^{4b} unabhängig Wasserstoff, Halogen, eine Alkoxygruppe mit 1 bis 6 Kohlenstoffatomen, eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen, Trifluormethyl, oder eine, ein Fluoratom enthaltende niedere Alkoxygruppe mit 1 bis 6 Kohlenstoffatomen ist.

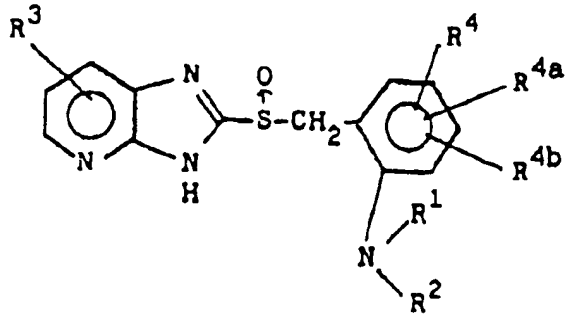
2. Sulfoxidderivat gemäß Anspruch 1, bei dem jeder von R^3, R^4, R^{4a} und R^{4b} Wasserstoff ist.

3. Sulfoxidderivat gemäß Anspruch 1, bei dem jeder von R^1 und R^2 unabhängig eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen ist.

4. Sulfoxidderivat gemäß Anspruch 1, bei dem jeder von R^1 und R^2 unabhängig Methyl oder Ethyl ist.

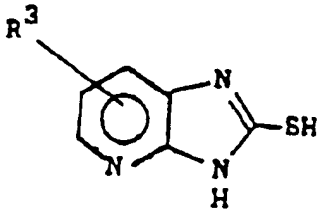
5. Sulfoxidderivat gemäß Anspruch 1, wobei das Derivat 2-(2-Dimethylaminobenzylsulfinyl)imidazo[4,5-b]pyridin ist.

6. Verfahren zur Herstellung eines Sulfoxidderivats mit der Formel (I) :



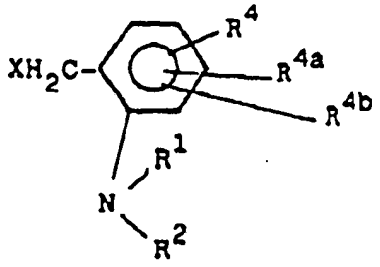
(I)

worin jeder von R^1 und R^2 unabhängig Wasserstoff oder eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen ist, und jeder von R^3, R^4, R^{4a} und R^{4b} unabhängig Wasserstoff, Halogen, eine Alkoxygruppe, die 1 bis 6 Kohlenstoffatome enthält, Trifluormethyl, oder eine ein Fluoratom enthaltende niedere Alkoxygruppe mit 1 bis 6 Kohlenstoffatomen, oder eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen ist, welches umfaßt : Reaktion eines Mercaptoderivats mit der Formel (II) :



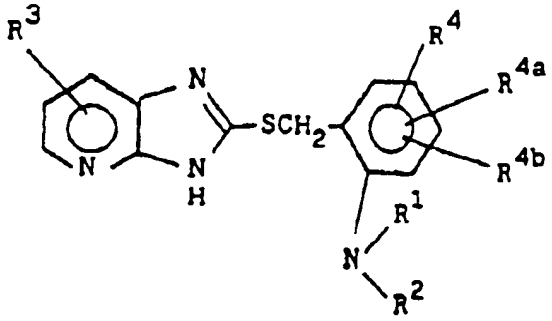
(II)

worin R^3 die gleiche Bedeutung wie oben hat, mit einer Verbindung, die die Formel (III) hat :



(III)

worin jeder von R^1, R^2, R^4, R^{4a} und R die gleiche Bedeutung wie oben hat, und worin X eine reaktive Gruppe ist, oder einem Salz davon, so daß man eine Verbindung mit der Formel (IV) erhält :



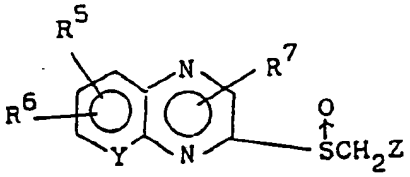
(IV)

worin jeder von R^1, R^2, R^3, R^4, R^{4a} und R^{4b} die gleiche Bedeutung wie oben hat, und Oxidation der Verbindung mit der Formel (IV).

7. Verfahren zur Herstellung eines Sulfoxidderivats gemäß Anspruch 6, bei dem die durch X in der Formel (III) dargestellte Gruppe ein Halogenatom, eine Sulfonylgruppe oder Acetoxy ist.

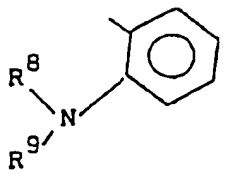
8. Verfahren zur Herstellung eines Sulfoxidderivats gemäß Anspruch 6, bei dem die Reaktion zwischen dem Mercaptoderivat der Formel (II) und der Verbindung der Formel (III) in einem inerten Lösungsmittel in der Gegenwart eines alkalischen Mittels durchgeführt wird.

9. Sulfoxidderivat mit der Formel (V) :



(V)

worin jeder von R^5 und R^6 unabhängig Wasserstoff, Halogen, eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen, oder eine Alkoxygruppe mit 1 bis 6 Kohlenstofffatomen, ist, R^7 Wasserstoff, eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen, oder eine Alkoxygruppe mit 1 bis 6 Kohlenstoffatomen ist, Y CH oder N ist, und Z ist : unsubstituiertes 2-Pyridyl ; oder 2-Pyridyl, das mit einem Halogen substituiert ist, eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen und/oder eine Alkoxygruppe mit 1 bis 6 Kohlenstoffatomen ; oder eine 2-Aminophenylgruppe mit d r Formel (VI) :



(VI)

worin jeder von R^8 und R^9 unabhängig Wasserstoff oder eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen ist, und die Phenylgruppe mit einem Halogen, einer Alkylgruppe mit 1 bis 6 Kohlenstoffatomen und/oder einer Alkoxygruppe mit 1 bis 6 Kohlenstoffatomen substituiert sein kann.

10. Sulfoxidderivat gemäß Anspruch 9, bei dem jeder von R^5, R^6 und R^7 unabhängig Wasserstoff oder Methyl ist.

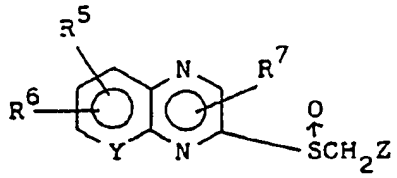
11. Sulfoxidderivat gemäß Anspruch 9, bei dem jeder von R^8 und R^9 unabhängig eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen ist.

12. Sulfoxidderivat gemäß Anspruch 9, bei dem jeder von R^8 und R^9 unabhängig mit Methyl oder Ethyl ist.

13. Sulfoxidderivat gemäß Anspruch 9, wobei das Derivat eines ist, ausgewählt aus der Gruppe, bestehend aus :

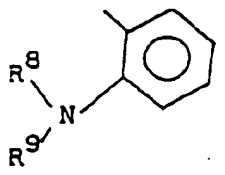
2-(2-Pyridylmethylsulfinyl)quinoxalin ;
3-Methyl-2-(pyridylmethylsulfinyl)quinoxalin ;
2-[2-(4-Methoxypyridyl)methylsulfinyl]-3-methyl-quinoxalin ;
3-Methyl-2- [2-(3-methylpyridyl)methylsulfinyl]-quinoxalin ;
6,7-Dimethyl-2-(2-pyridylmethylsulfinyl)quinoxalin ;
2-Methyl-3-(2-pyridylmethylsulfinyl)pyrido[2,3-b]-pyrazin ;
2-(2-Dimethylaminobenzylsulfinyl)quinoxalin ;
2-(2-Dimethylaminobenzylsulfinyl)-3-methyl-quinoxalin ;
2-(2-Dimethylaminobenzylsulfinyl)-3,6,7-trimethyl-quinoxalin ;
2-(2-Dimethylamino-3-methylbenzylsulfinyl)-3-methyl-quinoxalin ;
2-(2-Dimethylamino-5-methylbenzylsulfinyl)-3-methyl-quinoxalin ;
2-(2-Dimethylamino-5-methoxybenzylsulfinyl)-3-methyl-quinoxalin ; und
2-(2-Diethylaminobenzylsulfinyl)quinoxalin.

14. Verfahren zur Herstellung eines Sulfoxidderivats mit der Formel (V) :



(V)

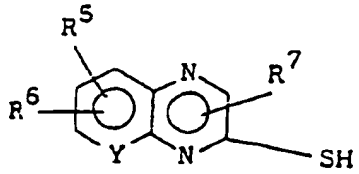
worin jeder von R^5 und R^6 unabhängig Wasserstoff, Halogen, eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen, oder eine Alkoxygruppe mit 1 bis 6 Kohlenstoffatomen ist, R^7 Wasserstoff, eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen, oder eine Alkoxygruppe mit 1 bis 6 Kohlenstoffatomen ist, Y CH oder N ist, und Z ist : unsubstituiertes 2-Pyridyl ; oder 2-Pyridyl, das mit einem Halogen substituiert ist, eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen und/oder eine Alkoxygruppe mit 1 bis 6 Kohlenstoffatomen ; oder eine 2-Aminophenylgruppe mit der Formel (VI) :



(VI)

worin jeder von R^8 und R^9 unabhängig Wasserstoff oder eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen ist, und die Phenylgruppe mit einem Halogen, einer Alkylgruppe mit 1 bis 6 Kohlenstoffatomen und/oder einer Alko-

xygruppe mit 1 bis 6 substituiert s in kann,
welches umfaßt:
Reaktion eines Mercaptoderivats mit der Form l (VII):

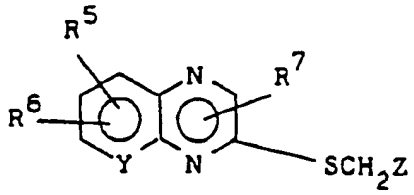


(VII)

worin jeder von R^5, R^6, R^7 und Y dieselbe Bedeutung wie oben hat, mit einer Verbindung, die die Formel (VIII) hat:

$$QCH_2Z$$

worin Z die gleiche Bedeutung wie oben hat und Q eine reaktive Gruppe ist, oder einem Salz davon, so daß man eine Verbindung mit der Formel (IX) erhält:



(IX)

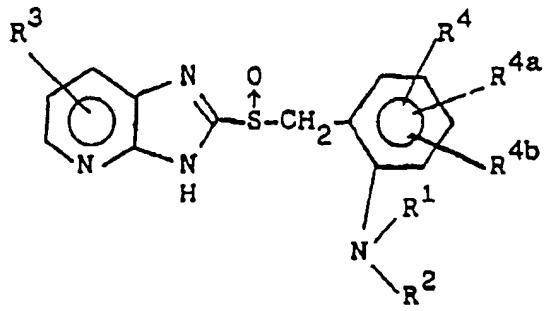
worin jeder von R^5, R^6, R^7, Y und Z die gleiche Bedeutung wie oben hat, und Oxidation der Verbindung mit der Formel (IX).

15. Verfahren zur Herstellung eines Sulfoxidderivats gemäß Anspruch 14, bei dem die durch Q in der Formel (VIII) dargestellte reaktive Gruppe ein Halogenatom, eine Sulfonylgruppe oder Acetoxy ist.

16. Verfahren zur Herstellung eines Sulfoxidderivats gemäß Anspruch 14, bei dem die Reaktion zwischen dem Mercaptoderivat der Formel (VII) und der Verbindung der Formel (VIII) in einem inerten Lösungsmittel in der Gegenwart eines alkalischen Mittels durchgeführt wird.

17. Pharmazeutische Zusammensetzung, die als aktiven Bestandteil ein Sulfoxidderivat mit Formel (I) oder (V) enthält:

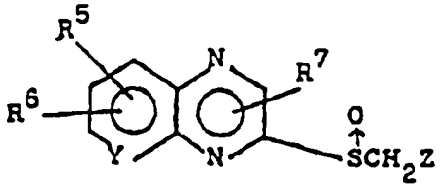
Formel (I)



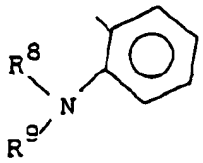
worin jeder v n R^1 und R^2 unabhängig Wasserstoff oder ine Alkylgrupp mit 1 bis 6 Kohl nstoffatom n ist, und jeder von R^3, R^4, R^{4a} und R^{4b} unabhängig Wasserstoff, Halogen eine Alkoxygruppe mit 1 bis 6 K hlen-

t ffatomen, Trifluormethyl, oder ein , ein Fluoratom enthalt nde niedere Alkoxygrupp mit 1 bis 6 Kohl nstoffatomen, oder ein Alkylgruppe mit 1 bis 6 Kohl nst ffatomen ist,

Formel (V)



worin jeder von R^5 und R^6 unabhängig Wasserstoff, Halogen, eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen, oder eine Alkoxygruppe mit 1 bis 6 Kohlenstoffatomen ist, R^7 Wasserstoff, eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen, oder eine Alkoxygruppe mit 1 bis 6 Kohlenstoffatomen ist, Y CH oder N und Z ist : unsubstituiertes 2-Pyridyl ; oder 2-Pyridyl, das mit einem Halogen substituiert ist, eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen und/oder eine Alkoxygruppe mit 1 bis 6 Kohlenstoffatomen ; oder eine 2-Aminophenylgruppe mit der Formel (VI) :

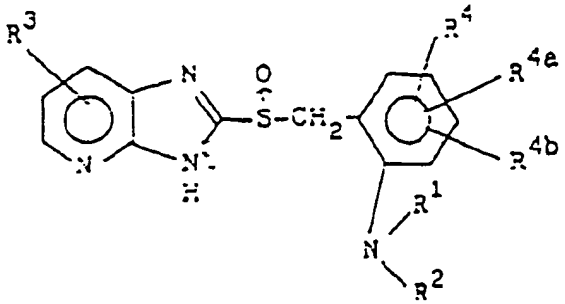


(VI)

worin jeder von R^8 und R^9 unabhängig Wasserstoff oder eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen ist, und die Phenylgruppe mit einem Halogen, eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen und/oder einer Alkoxygruppe mit 1 bis 6 Kohlenstoffatomen substituiert sein kann.

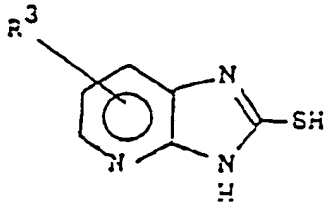
Patentansprüche für den Vertragsstaat : ES

1. Verfahren zur Herstellung eines Sulfoxidderivats mit der Formel (I) :



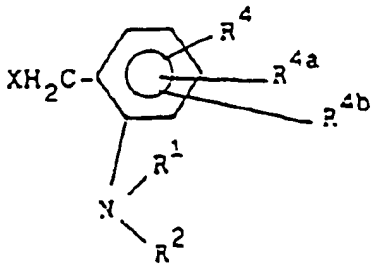
(I)

worin jeder von R^1 und R^2 unabhängig Wasserstoff oder eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen ist, und jeder von R^3, R^4, R^{4a} und R^{4b} unabhängig Wasserstoff, Halogen, eine Alkoxygruppe, die 1 bis 6 Kohlenstoffatome, Trifluormethyl enthält, oder eine, ein Fluoratom enthaltende nieder Alkoxygruppe mit 1 bis 6 Kohlenstoffatomen, oder eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen ist, welches umfaßt :
Reaktion ein s Mercaptod rivats mit d r Formel (II) :



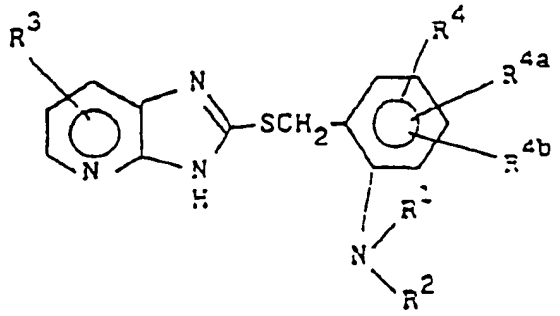
(II)

worin R^3 die gleiche Bedeutung wie oben hat, mit einer Verbindung mit der Formel (III):



(III)

worin jeder von R^1, R^2, R^4, R^{4a} und R^{4b} die gleiche Bedeutung wie oben hat, und X eine reaktive Gruppe ist, oder einem Salz davon, so daß man eine Verbindung mit der Formel (IV) erhält:



(IV)

worin jeder von R^1, R^2, R^3, R^4, R^{4a} und R^{4b} die gleiche Bedeutung wie oben hat, und Oxidation der Verbindung mit der Formel (IV).

2. Verfahren zur Herstellung eines Sulfoxidderivats gemäß Anspruch 1, bei dem die durch X in der Formel (III) dargestellte reaktive Gruppe ein Halogenatom, eine Sulfonylgruppe oder Acetoxy ist.

3. Verfahren zur Herstellung eines Sulfoxidderivats gemäß Anspruch 6, bei dem die Reaktion zwischen dem Mercaptoderivat der Formel (II) und der Verbindung der Formel (III) in einem inerten Lösungsmittel in der Gegenwart eines alkalischen Mittels durchgeführt wird.

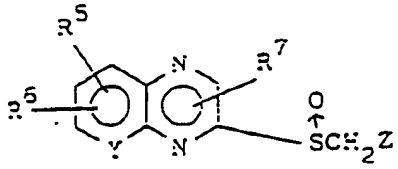
4. Verfahren zur Herstellung eines Sulfoxidderivats gemäß Anspruch 1, bei dem jeder von R^3, R^4, R^{4a} uns R^{4b} Wasserstoff ist.

5. Verfahren zur Herstellung eines Sulfoxidderivats gemäß Anspruch 1, bei dem jeder von R^1 und R^2 unabhängig eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen ist.

6. Verfahren zur Herstellung eines Sulfoxidderivats gemäß Anspruch 1, bei dem jeder von R^1 und R^2 einzeln Methyl oder Ethyl ist.

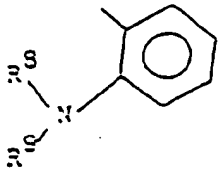
7. Verfahren zur Herstellung eines Sulfoxidderivats gemäß Anspruch 1, wobei das Derivat 2-(2-Dimethylaminobenzylsulfinyl)imidazo [4,5-b] pyridin ist.

8. Verfahren zur Herstellung eines Sulfoxidderivats mit der Formel (V):



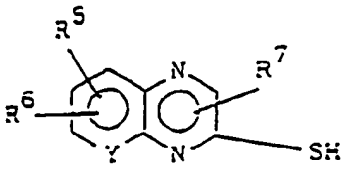
(V)

worin jeder von R^5 und R^6 unabhängig Wasserstoff, Halogen, eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen, oder eine Alkoxygruppe mit 1 bis 6 Kohlenstoffatomen, ist, R^7 Wasserstoff, eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen, oder eine Alkoxygruppe mit 1 bis 6 Kohlenstoffatomen ist, Y CH oder N ist, und Z ist : unsubstituiertes 2-Pyridyl ; oder 2-Pyridyl, das mit einem Halogen substituiert ist, eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen und/oder eine Alkoxygruppe mit 1 bis 6 Kohlenstoffatomen ; oder eine 2-Aminophenylgruppe mit der Formel (VI) :



(VI)

worin jeder von R^8 und R^9 unabhängig Wasserstoff oder eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen ist, und die Phenylgruppe mit einem Halogen, einer Alkylgruppe mit 1 bis 6 Kohlenstoffatomen und/oder einer Alkoxygruppe mit 1 bis 6 Kohlenstoffatomen substituiert sein kann, welches umfaßt : Reaktion eines Mercaptoderivats mit der Formel (VII) :

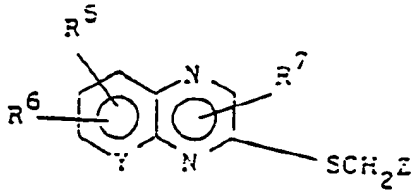


(VII)

worin jeder von R^5, R^6, R^7 und Y die gleiche Bedeutung wie oben hat, mit einer Verbindung mit der Formel (VIII) :

$$QCH_2Z$$

worin Z die gleiche Bedeutung wie oben hat, und Q reaktive Gruppe ist, oder einem Salz davon, so daß man eine Verbindung mit der Formel (IX) erhält :



(IX)

worin j der von R^5, R^6, R^7, Y und Z die gleich Bedeutung wi oben hat, und Oxidation der Verbindung mit der Form l (IX).

9. Verfahren zur Herstellung eines Sulfoxidderivats gemäß Anspruch 8, bei dem di durch Q in der Formel

(VIII) dargestellte Gruppe ein Halogenatom, eine Sulfonylgruppe oder Acetoxy ist.

10. Verfahren zur Herstellung eines Sulfoxidderivats gemäß Anspruch 8, bei dem die Reaktion zwischen dem Mercaptoderivat der Formel (VII) und der Verbindung der Formel (VIII) in einem inerten Lösungsmittel in der Gegenwart eines alkalischen Mittels durchgeführt wird.

11. Verfahren zur Herstellung eines Sulfoxidderivats gemäß Anspruch 8, bei dem jeder von R^5, R^6 und R^7 unabhängig Wasserstoff oder Methyl ist.

12. Verfahren zur Herstellung eines Sulfoxidderivats gemäß Anspruch 8, bei dem jeder von R^8 und R^9 unabhängig einer Alkylgruppe mit 1 bis 6 Kohlenstoffatomen ist.

13. Verfahren zur Herstellung eines Sulfoxidderivats gemäß Anspruch 8, bei dem jeder von R^8 und R^9 unabhängig Methyl oder Ethyl ist.

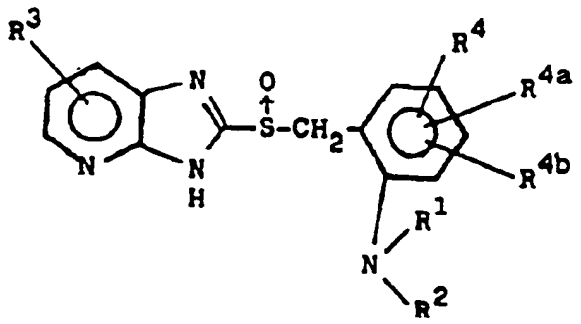
14. Verfahren zur Herstellung eines Sulfoxidderivats gemäß Anspruch 8, wobei das Derivat eines ist, ausgewählt aus der Gruppe, bestehend aus :

2-(2-Pyridylmethylsulfinyl)quinoxalin ;
3-Methyl-2-(pyridylmethylsulfinyl)quinoxalin ;
2-[2-(4-Methoxypyridyl)methylsulfinyl]-3-methyl-quinoxalin ;
3-Methyl-2-[2-(3-methylpyridyl)methylsulfinyl]-quinoxalin ;
6,7-Dimethyl-2-(2-pyridylmethylsulfinyl)quinoxalin ;
2-Methyl-3-(2-pyridylmethylsulfinyl)pyrido[2,3-b]-pyrazin ;
2-(2-Dimethylaminobenzylsulfinyl)quinoxalin ;
2-(2-Dimethylaminobenzylsulfinyl)-3-methyl-quinoxalin ;
2-(2-Dimethylaminobenzylsulfinyl)-3,6,7-trimethhyl-quinoxalin ;
2-(2-Dimethylamino-3-methylbenzylsulfinyl)-3-methyl-quinoxalin ;
2-(2-Dimethylamino-5-methylbenzylsulfinyl)-3-methyl-quinoxalin ;
2-(2-Dimethylamino-5-methoxybenzylsulfinyl)-3-methyl-quinoxalin ; und
2-(2-Diethylaminobenzylsulfinyl)quinoxalin.

Revendications

Revendications pour les Etats contractants : BE, CH, DE, FR, GB, IT, LI, NL, SE

1. Sulfoxyde répondant à la formule (I)



(I)

dans laquelle chacun de R^1 et R^2 est indépendamment l'hydrogène ou un groupe alkyle ayant 1 à 6 atomes de carbone, et chacun de R^3, R^4, R^{4a} et R^{4b} est indépendamment l'hydrogène, un halogène, un groupe alcoxy ayant 1 à 6 atomes de carbone, un groupe alkyle ayant 1 à 6 atomes de carbone, le groupe trifluorométhyle ou un groupe alcoxy inférieur ayant 1 à 6 atomes de carbone et contenant un ou plusieurs atomes de fluor.

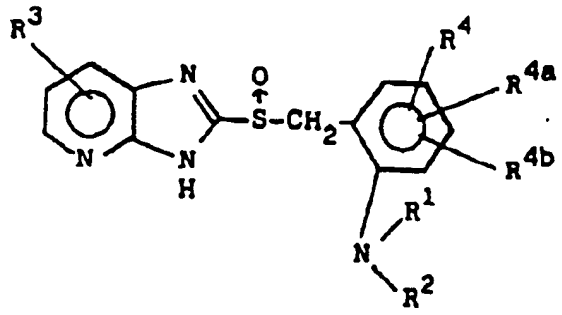
2. Sulfoxyde selon la revendication 1, dans lequel chacun de R^3, R^4, R^{4a} et R^{4b} est l'hydrogène.

3. Sulfoxyde selon la revendication 1, dans lequel chacun de R^1 et R^2 est indépendamment un groupe alkyle ayant 1 à 6 atomes de carbone.

4. Sulfoxyde selon la revendication 1, dans lequel chacun de R^1 et R^2 est indépendamment un groupe méthyle ou éthyle.

5. Sulfoxyde selon la revendication 1, dans lequel ledit sulfoxyde est la 2-(2-diméthylaminobenzylsulfinyl)imidaz [4,5-b]pyridine.

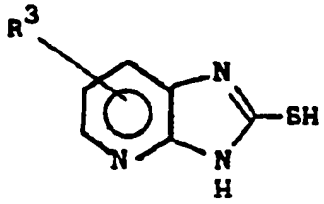
6. Procédé de préparation d'un sulfoxyde répondant à la formule (I) :



(I)

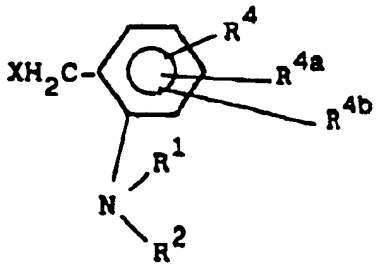
dans laquelle chacun de R^1 et R^2 est indépendamment l'hydrogène ou un groupe alkyle ayant 1 à 6 atomes de carbone, et chacun de R^3, R^4, R^{4a} et R^{4b} est indépendamment l'hydrogène, un halogène, un groupe alcoxy ayant 1 à 6 atomes de carbone, le groupe trifluorométhyle ou un groupe alcoxy inférieur ayant 1 à 6 atomes de carbone et contenant un ou plusieurs atomes de fluor, ou un groupe alkyle ayant 1 à 6 atomes de carbone, qui consiste à :

faire réagir un mercaptan répondant à la formule (II) :



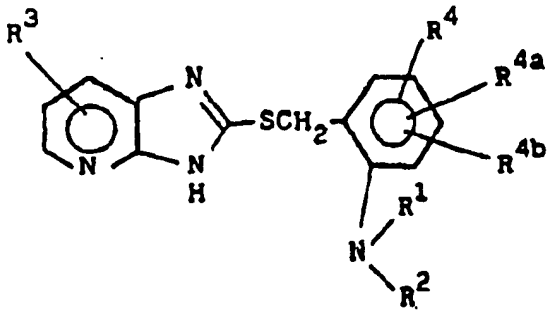
(II)

dans laquelle R^3 est tel que défini ci-dessus, avec un composé répondant à la formule (III) :



(III)

dans laquelle chacun de R^1, R^2,R^4,R^{4a} et R^{4b} est tel que défini ci-dessus, et X est un groupe réactif, ou un sel de celui-ci, pour obtenir un composé répondant à la formule (IV) :



(IV)

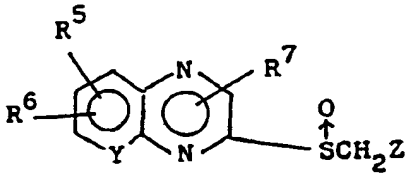
dans laquelle chacun de R^1, R^2, R^3, R^4, R^{4a} et R^{4b} est tel que défini ci-dessus, et

oxyder le composé de formule (IV).

7. Procédé de préparation d'un sulfoxyde selon la revendication 6, dans lequel ledit groupe réactif représenté par X dans la formule (III) est un atome d'halogène, un groupe sulfonyle ou acétoxy.

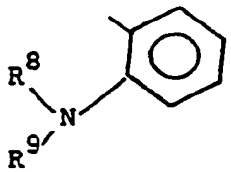
8. Procédé de préparation d'un sulfoxyde selon la revendication 6, dans lequel ladite réaction entre le mercaptan de formule (II) et le composé de formule (III) est effectuée dans un solvant inerte en présence d'un agent alcalin.

9. Sulfoxyde répondant à la formule (V) :



(V)

dans laquelle chacun de R^5 et R^6 est indépendamment l'hydrogène, un halogène, un groupe alkyle ayant 1 à 6 atomes de carbone ou un groupe alcoxy ayant 1 à 6 atomes de carbone, R^7 est l'hydrogène, un groupe alkyle ayant 1 à 6 atomes de carbone ou un groupe alcoxy ayant 1 à 6 atomes de carbone, Y est CH ou N, et Z est: un groupe 2-pyridyle non substitué ; ou un groupe 2-pyridyle substitué par un halogène, un groupe alkyle ayant 1 à 6 atomes de carbone et/ou un groupe alcoxy ayant 1 à 6 atomes de carbone ; ou un groupe 2-aminophényle répondant à la formule (VI) :



(VI)

dans laquelle chacun de R^8 et R^9 est indépendamment l'hydrogène ou un groupe alkyle ayant 1 à 6 atomes de carbone, et le groupe phényle peut être substitué par un halogène, un groupe alkyle ayant 1 à 6 atomes de carbone et/ou un groupe alcoxy ayant 1 à 6 atomes de carbone.

10. Sulfoxyde selon la revendication 9, dans lequel chacun de R^5, R^6 et R^7 est indépendamment un atome d'hydrogène ou un groupe méthyle.

11. Sulfoxyde selon la revendication 9, dans lequel chacun de R^8 et R^9 est indépendamment un groupe alkyle ayant 1 à 6 atomes de carbone.

12. Sulfoxyde selon la revendication 9, dans lequel chacun de R^8 et R^9 est indépendamment un groupe méthyle ou éthyle.

13. Sulfoxyde selon la revendication 9, dans lequel ledit sulfoxyde est choisi dans le groupe formé par :

la 2-(2-pyridylméthylsulfinyl)quinoxaline ;

la 3-méthyl-2-(2-pyridylméthylsulfinyl)-quinoxaline ;

la 2-[2-(4-méthoxypyridyl)méthylsulfinyl]-3-méthylquinoxaline ;

la 3-méthyl-2-[2-(3-méthylpyridyl)méthyl-sulfinyl]quinoxaline ;

la 6,7-diméthyl-2-(2-pyridylméthylsulfinyl)-quinoxaline ;

la 2-méthyl-3-(2-pyridylméthylsulfinyl)pyrido-[2,3-b]pyrazine ;

la 2-(2-diméthylaminobenzylsulfinyl)quinoxaline ;

la 2-(2-diméthylaminobenzylsulfinyl)-3-méthyl-quinoxaline ;

la 2-(2-diméthylaminobenzylsulfinyl)-3,6,7-triméthylquinoxaline ;

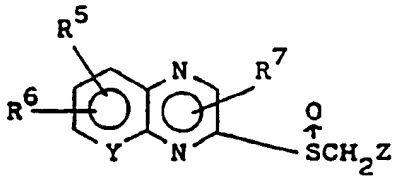
la 2-(2-diméthylamino-3-méthylbenzylsulfinyl)-3-méthylquinoxaline ;

la 2-(2-diméthylamino-5-méthylbenzylsulfinyl)-3-méthylquinoxaline ;

la 2-(2-diméthylamino-5-méthoxybenzylsulfinyl)-3-méthylquinoxaline ; et

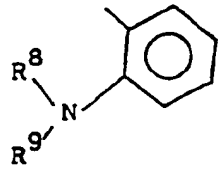
la 2-(2-diéthylamino benzylsulfinyl)quinoxaline .

14. Procédé de préparation d'un sulfoxyde répondant à la formule (V) :



(V)

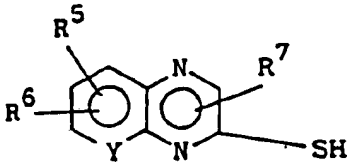
dans laquelle chacun de R^5 et R^6 est indépendamment l'hydrogène, un halogène, un groupe alkyle ayant 1 à 6 atomes de carbone ou un groupe alcoxy ayant 1 à 6 atomes de carbone, R^7 est l'hydrogène, un groupe alkyle ayant 1 à 6 atomes de carbone ou un groupe alcoxy ayant 1 à 6 atomes de carbone, Y est CH ou N, et Z est: un groupe 2-pyridyle non substitué ; ou un groupe 2-pyridyle substitué par un halogène, un groupe alkyle ayant 1 à 6 atomes de carbone et/ou un groupe alcoxy ayant 1 à 6 atomes de carbone ; ou un groupe 2-aminophényle répondant à la formule (VI) :



(VI)

dans laquelle chacun de R^8 et R^9 est indépendamment l'hydrogène ou un groupe alkyle ayant 1 à 6 atomes de carbone, et le groupe phényle peut être substitué par un halogène, un groupe alkyle ayant 1 à 6 atomes de carbone et/ou un groupe alcoxy ayant 1 à 6 atomes de carbone ; qui consiste à :

faire réagir un mercaptan répondant la formule générale (VII) :

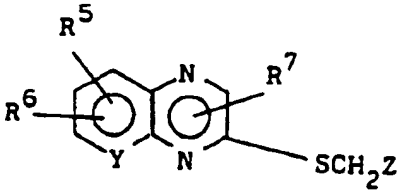


(VII)

dans laquelle chacun de R^5, R^6, R^7 et Y est tel que défini ci-dessus, avec un composé répondant à la formule (VIII) :

$$QCH_2Z \quad \text{(VIII)}$$

dans laquelle Z est tel que défini ci-dessus et Q est un groupe réactif,
ou un sel de celui-ci, pour obtenir un composé répondant à la formule (IX) :



(IX)

dans laquelle chacun de R^5, R^6, R^7, Y et Z est tel que défini ci-dessus, et

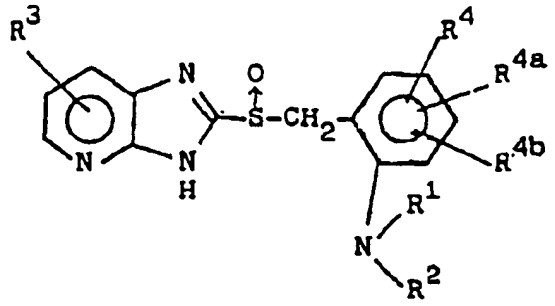
oxyder le composé de formule (IX).

15. Procédé de préparation d'un sulfoxyde selon la revendication 14, dans lequel ledit groupe réactif représenté par Q dans la formule (VIII) est un atom d'halogène, un groupe sulfonyle ou acétoxy.

16. Procédé de préparation d'un sulf xyde selon la revendication 14, dans lequ l ladite réaction entre l mercaptan de formul (VII) et le composé de formul (VIII) est eff ctuée dans un solvant inerte n prés nce d'un agent alcalin.

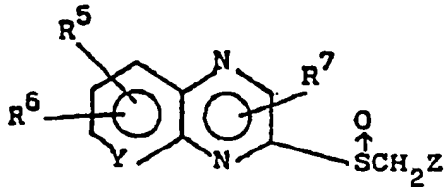
17. Compositi n pharmaceutique contenant comme ingrédi nt actif un sulfoxyde répondant à la formule (I) ou (V) :

formule (I)

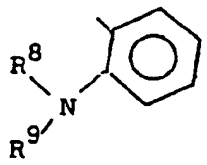


dans laquelle chacun de R^1 et R^2 est indépendamment l'hydrogène ou un groupe alkyle ayant 1 à 6 atomes de carbone, et chacun de R^3, R^4, R^{4a} et R^{4b} est indépendamment l'hydrogène, un halogène, un groupe alcoxy ayant 1 à 6 atomes de carbone, le groupe trifluorométhyle ou un groupe alcoxy inférieur ayant 1 à 6 atomes de carbone et contenant un ou plusieurs atomes de fluor, ou un groupe alkyle ayant 1 à 6 atomes de carbone,

formule (V)



dans laquelle chacun de R^5 et R^6 est indépendamment l'hydrogène, un halogène, un groupe alkyle ayant 1 à 6 atomes de carbone ou un groupe alcoxy ayant 1 à 6 atomes de carbone, R^7 est l'hydrogène, un groupe alkyle ayant 1 à 6 atomes de carbone ou un groupe alcoxy ayant 1 à 6 atomes de carbone, Y est CH ou N, et Z est: un groupe 2-pyridyle non substitué ; ou un groupe 2-pyridyle substitué par un halogène, un groupe alkyle ayant 1 à 6 atomes de carbone et/ou un groupe alcoxy ayant 1 à 6 atomes de carbone ; ou un groupe 2-aminophényle répondant à la formule (VI) :

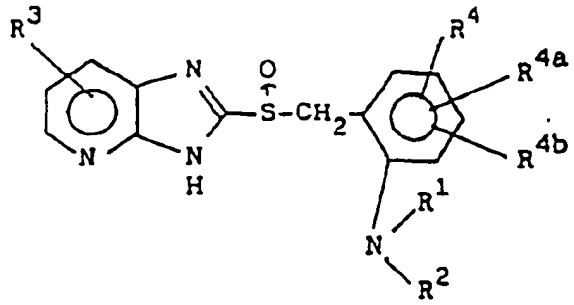


(VI)

dans laquelle chacun de R^8 et R^9 est indépendamment l'hydrogène ou un groupe alkyle ayant 1 à 6 atomes de carbone, et le groupe phényle peut être substitué par un halogène, un groupe alkyle ayant 1 à 6 atomes de carbone et/ou un groupe alcoxy ayant 1 à 6 atomes de carbone.

Rev ndicati ns pour l'Etat C ntractant : ES

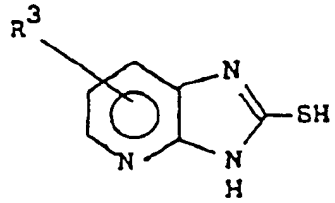
1. Procédé d préparati n d'un sulfoxyd répondant à la f rmule (I) :



(I)

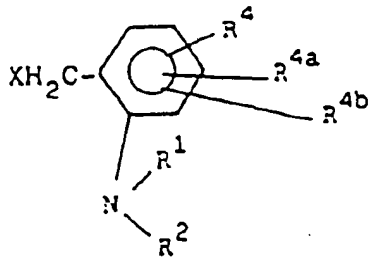
dans laquelle chacun de R^1 et R^2 est indépendamment l'hydrogène ou un groupe alkyle ayant 1 à 6 atomes de carbone, et chacun de R^3, R^4, R^{4a} et R^{4b} est indépendamment l'hydrogène, un halogène, un groupe alcoxy ayant 1 à 6 atomes de carbone, le groupe trifluorométhyle ou un groupe alcoxy inférieur ayant 1 à 6 atomes de carbone et contenant un ou plusieurs atomes de fluor, ou un groupe alkyle ayant 1 à 6 atomes de carbone, qui consiste à :

faire réagir un mercaptan répondant à la formule (II) :



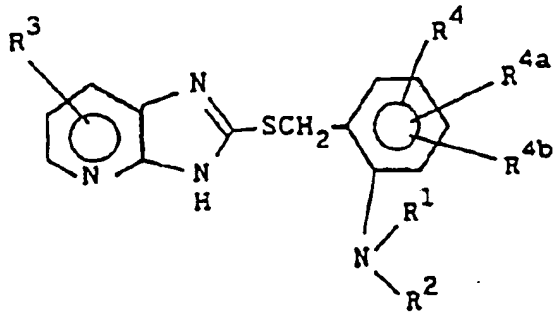
(II)

dans laquelle R^3 est tel que défini ci-dessus, avec un composé répondant à la formule (III) :



(III)

dans laquelle chacun de R^1, R^2, R^4 R^{4a}et R^{4b} est tel que défini ci-dessus, et X est un groupe réactif, ou un sel de celui-ci, pour obtenir un composé répondant à la formule (IV) :



(IV)

dans laquelle chacun de R^1, R^2, R^3, R^4, R^{4a} et R^{4b} est tel que défini ci-dessus, et

oxyder le composé de formule (IV).

2. Procédé de préparation d'un sulfoxyde selon la revendication 1, dans lequel ledit groupe réactif représenté par X dans la formule (III) est un atome d'halogène, un groupe sulfonyle ou acétoxy.

3. Procédé de préparation d'un sulfoxyde selon la revendication 1, dans lequel ladite réaction entre le mercaptan de formule (II) et le composé de formule (III) est effectuée dans un solvant inerte en présence d'un agent alcalin.

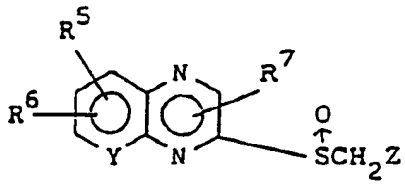
4. Procédé de préparation d'un sulfoxyde selon la revendication 1, dans lequel chacun de R^3, R^4, R^{4a} et R^{4b} est l'hydrogène.

5. Procédé de préparation d'un sulfoxyde selon la revendication 1, dans lequel chacun de R^1 et R^2 est indépendamment un groupe alkyle ayant 1 à 6 atomes de carbone.

6. Procédé de préparation d'un sulfoxyde selon la revendication 1, dans lequel chacun de R^1 et R^2 est indépendamment un groupe méthyle ou éthyle.

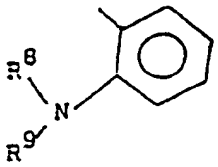
7. Procédé de préparation d'un sulfoxyde selon la revendication 1, dans lequel ledit sulfoxyde est la 2-(2-diméthylaminobenzylsulfinyl)imidazo[4,5-b]pyridine.

8. Procédé de préparation d'un sulfoxyde répondant à la formule (V) :



(V)

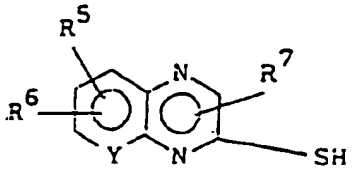
dans laquelle chacun de R^5 et R^6 est indépendamment l'hydrogène, un halogène, un groupe alkyle ayant 1 à 6 atomes de carbone ou un groupe alcoxy ayant 1 à 6 atomes de carbone, R^7 est l'hydrogène, un groupe alkyle ayant 1 à 6 atomes de carbone ou un groupe alcoxy ayant 1 à 6 atomes de carbone, Y est CH ou N, et Z est: un groupe 2-pyridyle non substitué ; ou un groupe 2-pyridyle substitué par un halogène, un groupe alkyle ayant 1 à 6 atomes de carbone et/ou un groupe alcoxy ayant 1 à 6 atomes de carbone ; ou un groupe 2-aminophényle répondant à la formule (VI) :



(VI)

dans laquelle chacun de R^8 et R^9 est indépendamment l'hydrogène ou un groupe alkyle ayant 1 à 6 atomes de carbone, et le groupe phényle peut être substitué par un halogène, un groupe alkyle ayant 1 à 6 atomes de carbone et/ou un groupe alcoxy ayant 1 à 6 atomes de carbone ; qui consiste à :

faire réagir un mercaptan répondant la formule générale (VII) :



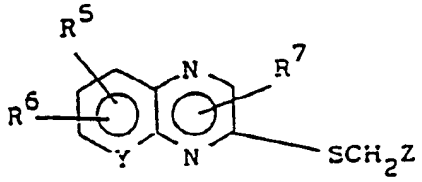
(VII)

dans laquelle chacun de R^5, R^6, R^7 et Y est tel que défini ci-dessus, avec un composé répondant à la formule (VIII) :

$$QCH_2Z \quad \text{(VIII)}$$

dans laquelle Z est tel que défini ci-dessus et Q est un groupe réactif, ou un sel de celui-ci, pour obtenir un

composé répondant à la formule (IX) :



(IX)

dans laquelle chacun de R^5, R^6, R^7, Y et Z est tel que défini ci-dessus, et

oxyder le composé de formule (IX).

9. Procédé de préparation d'un sulfoxyde selon la revendication 8, dans lequel ledit groupe réactif représenté par Q dans la formule (VIII) est un atome d'halogène, un groupe sulfonyle ou acétoxy.

10. Procédé de préparation d'un sulfoxyde selon la revendication 8, dans lequel ladite réaction entre le mercaptan de formule (VII) et le composé de formule (VIII) est effectuée dans un solvant inerte en présence d'un agent alcalin.

11. Procédé de préparation d'un sulfoxyde selon la revendication 8, dans lequel chacun de R^5, R^6 et R^7 est l'hydrogène ou un groupe méthyle.

12. Procédé de préparation d'un sulfoxyde selon la revendication 8, dans lequel chacun de R^8 et R^9 est indépendamment un groupe alkyle ayant 1 à 6 atomes de carbone.

13. Procédé de préparation d'un sulfoxyde selon la revendication 8, dans lequel chacun de R^8 et R^9 est indépendamment un groupe méthyle ou éthyle.

14. Procédé de préparation d'un sulfoxyde selon la revendication 8, dans lequel ledit sulfoxyde est choisi dans le groupe formé par :

la 2-(2-pyridylméthylsulfinyl)quinoxaline ;
la 3-méthyl-2-(2-pyridylméthylsulfinyl)-quinoxaline ;
la 2-[2-(4-méthoxypyridyl)méthylsulfinyl]-3-méthylquinoxaline ;
la 3-méthyl-2-[2-(3-méthylpyridyl)méthylsulfinyl]-quinoxaline ;
la 6,7-diméthyl-2-(2-pyridylméthylsulfinyl)-quinoxaline ;
la 2-méthyl-3-(2-pyridylméthylsulfinyl)pyrido-[2,3-b]pyrazine ;
la 2-(2-diméthylaminobenzylsulfinyl)quinoxaline ;
la 2-(2-diméthylaminobenzylsulfinyl)-3-méthyl-quinoxaline ;
la 2-(2-diméthylaminobenzylsulfinyl)-3,6,7-triméthylquinoxaline ;
la 2-(2-diméthylamino-3-méthylbenzylsulfinyl)-3-méthylquinoxaline ;
la 2-(2-diméthylamino-5-méthylbenzylsulfinyl)-3-méthylquinoxaline ;
la 2-(2-diméthylamino-5-méthoxybenzylsulfinyl)-3-méthylquinoxaline ; et
la 2-(2-diéthylaminobenzylsulfinyl)quinoxaline.